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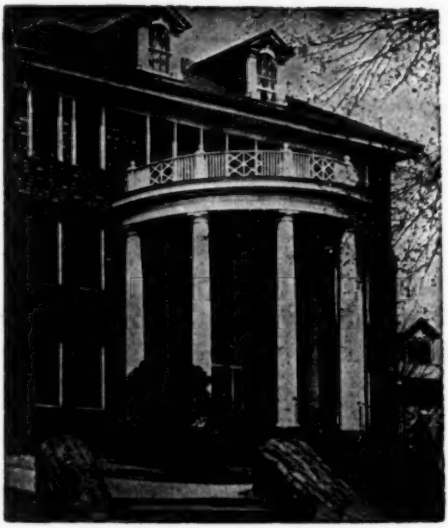

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AN ACTIVATING SYSTEM IN BRAIN STEM OF MONKEY

J. D. FRENCH, M.D.
F. K. VON AMERONGEN, M.D.
AND
H. W. MAGOUN, Ph.D.
LONG BEACH, CALIF.

THE EXISTENCE of afferent collateral pathways to areas of the brain stem and diencephalon medial to the well-known long projection systems has been demonstrated anatomically [1] and physiologically.[2] Recently, Starzl, Taylor, and Magoun [3] have shown in the cat that this centrally oriented core, comprising the midbrain tegmentum, the subthalamus and hypothalamus, and the ventromedial portion of the thalamus, forms a highly integrated system, in the extent of which single shock-evoked potentials of somatic and auditory origin can be recorded from collaterals which leave the median and lateral lemnisci as high as the posterior part of the thalamus. High-frequency stimulation of the peripheral receptors, on the other hand, effected desynchronization of electrical activity in this central core, as well as in the cortex. Furthermore, Moruzzi and Magoun [4] demonstrated that direct high-frequency stimulation of this medial system desynchronized electrocortical activity in a manner exactly paralleling arousal from sleep or alerting to attention.

This evidence indicated the presence of an activating system in the cephalic portion of the brain stem of the cat by means of which the arousing or alerting influences

This study was aided by a grant from the Commonwealth Fund.

Dr. T. E. Starzl and Dr. D. G. Whitlock gave assistance in the experiments, and Miss Cora Rucker prepared the brains for microscopic study.

From the Veterans Administration Hospital, Long Beach, Calif., and the Departments of Surgery and Anatomy, University of California School of Medicine at Los Angeles.

Reviewed in the Veterans Administration and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

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4. Moruzzi, G., and Magoun, H. W.: Brain Stem Reticular Formation and Activation of the EEG, Electroencephalog. & Clin. Neurophysiol. **1**:455-473 (Nov.) 1949.

of afferent stimulation might be exerted. The present experiments reveal the existence of a similar system in the monkey. Moreover, it is shown to be responsive to stimuli of visceral and visual origin, in addition to those mediated by the auditory and somatic systems.

PROCEDURE

Experiments were made on 10 monkeys (Macacus mulatus), prepared under ether, with exposure margins infiltrated with procaine. The animals were immobilized with decamethonium bromide (syncurine®) and maintained on artificial respiration. Clicks were employed for auditory stimulation. Single-shock condenser discharges with a falling phase of 1 msec. and a usual voltage of 5 were delivered from a Goodwin stimulator to the central end of the cut sciatic, splanchnic, or vagus nerve through shielded electrodes, and to the optic nerve (after evisceration of the globe) through a concentric bipolar needle electrode. As a check on the validity of visual responses, recordings were also made during stimulation of the intact eye with a strong flashlight. Screw electrodes in the calvara, and occasionally concentric electrodes directly applied, recorded from functional cortical areas; and needle electrodes inserted through a small craniotomy aperture and oriented with the Horsley-Clarke instrument served to record from the brain stem.

Repetitive stimuli (5 volts, 100 per second, 1 msec.) were delivered both to peripheral nerves and to the brain stem, in the latter isntance with the electrode oriented by means of the Horsley-Clarke instrument. Alteration in electrical activity following stimulation of peripheral nerves was recorded in the brain stem, as well as in the cortex, and electrocortical change was observed on stimulation of various areas in the brain stem. An eight-channel Grass amplifier and ink writer were employed for recording. All brains were worked up histologically for localization of electrode placement.

RESULTS

In the cephalic portion of the brain stem, a region comprising the midbrain tegmentum, the subthalamus, and hypothalamus, and the medial portion of the thalamus was distinguished, within which evoked potentials were recorded upon somatic, visceral, auditory, and visual stimulation. Single potentials in the medially situated system were of amplitude comparable to those recorded in the adjacent lateral sensory pathways, but responses to repetitive stimuli in the two areas were quite different. Succeeding responses were attenuated in the medial area when stimuli to the same peripheral source were introduced rapidly (Fig. 1 *A, I*). Similarly, interaction between responses evoked by stimuli to two different sources occurred when the second stimulus was inserted closely after the first. Thus, a click response was altered, attenuated, or even obliterated, when closely preceded by a sciatic response, and vice versa (Fig. 1 *F, H, J*). The potential evoked by a click stimulus was likewise much impaired when it immediately followed a splanchnic response, and vice versa (Fig. 1 *B, C, D, E*). The response to visual stimulation was greatly diminished when evoked soon after a click potential (Fig. 2 *A*). Such interaction or attenuation was characteristic of responses to peripheral stimulation in the medial area. In the lateral sensory pathways and relay nuclei, however, such interaction and attenuation did not occur. Here, rapidly interposed potentials from the same source of a frequency which would cause succeeding responses to be attenuated in the central core were evoked with unimpaired intensity (Fig. 1 *M*). Similarly, evoked potentials of different origins did not interact when recorded in the long sensory pathways (Fig. 1 *L, N*).

The areas in the cephalic portion of the brain stem from which evoked potentials of all modalities were recorded were strikingly similar in extent, being limited for the most part to the central core. Included were the midbrain tegmentum and the adjacent periaqueductal gray substance, the subthalamus and hypothalamus, and the

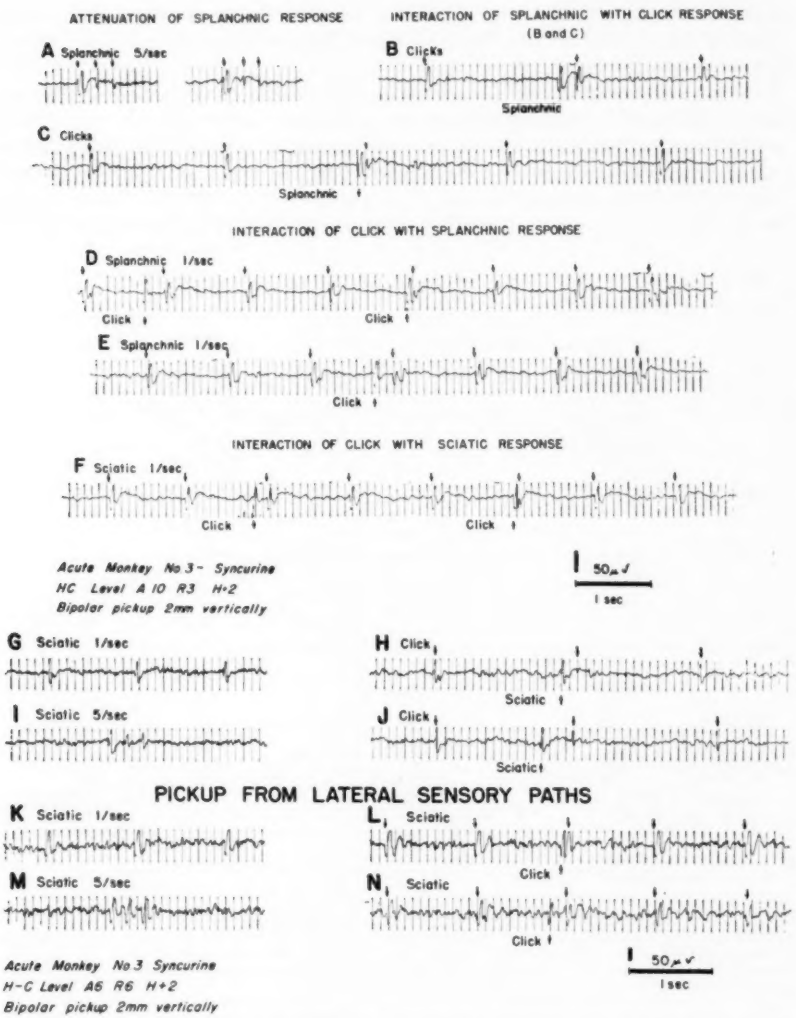

Fig. 1.—Evoked potentials are recorded in the reticular activating system (*G*, *I*) and lateral sensory pathways (*K*, *M*) from stimulation of the sciatic nerve. Such potentials when rapidly repetitive are attenuated in the former, but not in the latter, areas. Evoked potentials from click and sciatic stimuli are recorded in the reticular activating system (*F*, *H*, *J*) and lateral sensory pathways (*L*, *N*). When these potentials closely approximate one another, the succeeding stimulus is altered (interaction) in the former region (*F*, *H*, and *J*), but not in the latter (*L*, *N*). Similar interaction between click and splanchnic responses in the activating area is illustrated in (*B*, *C*, *D*, and *E*).

ventromedial part of the thalamus. The shaded areas in Figures 3 and 4 indicate the region in which responses were regularly recorded. It was not possible to record evoked potentials in the medial brain-stem core from stimulation of the vagus nerve in the two animals tested.

In the posterior extent of the explored area, at a vertical level through the rostral part of the tectum, evoked potentials were recorded upon auditory, visual, and somatic stimuli from the medial lemniscus to the dorsal portion of the central gray matter (Fig. 3 *E*) and, in the case of visual impulses, into the superior colliculi (Fig. 4 *D*). Mediolaterally, the receptive area extended from the midline to the lateral lemniscus. Discharge upon splanchnic-nerve stimulation was not apparent

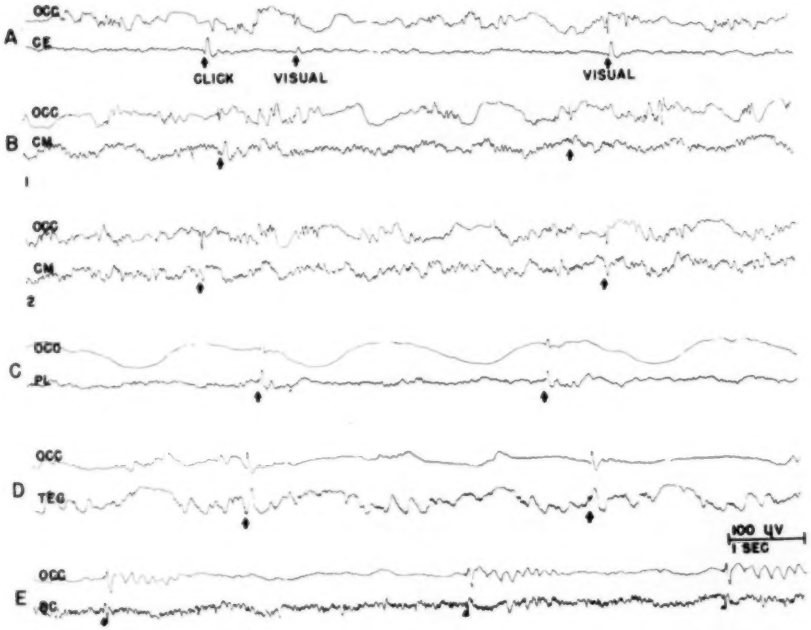

Fig. 2.—Visual collateral potentials are recorded during stimulation of the optic nerve from nucleus centralis medialis (*A*); the centrum medianum (*B*), in which phase reversal is shown as the recording electrode descended; the pulvinar (*C*); the midbrain tegmentum (*D*), and the brachium conjunctivum (*E*). The upper tracing of each pair is recorded from the primary visual cortex (*OCC*).

in the extreme posterior portion of the shaded area seen in Figure 3 but elsewhere was as richly represented as were other modalities. Potentials from stimulation of the optic nerve were recorded in a small area of the lateral inferior portion of the pulvinar (Fig. 2 *C*), as well as in the tegmentum (Figs. 2 *D* and 4 *D*). At a vertical level transecting the posterior third of the thalamus, the main body of response for all modalities extended from the substantia nigra to the inferior portion of the medial thalamic nucleus and from the midline, laterally, to the somatic relay nuclei (Figs. 3 *D* and 4 *C*). Here, all responses were regularly recorded in the tegmentum

and in the centrum medianum and the parafascicular and ventromedial nuclei of the thalamus. Occasionally, potentials were evoked more extensively in the medial nucleus on splanchnic and somatic stimulation and in the lateral nucleus upon auditory stimuli.

At a level just in front of the mamillary bodies, the receptive area for stimuli delivered to the auditory, somatic, and visceral systems was smaller in extent and comprised the dorsal portion of the posterior part of the hypothalamus, the midline thalamic nuclei, and the medioventral portion of the nucleus ventralis anterior (Figs. 3 *C* and 4 *B*). Occasional sciatic and auditory responses were recorded elsewhere in isolated portions of the ventral anterior and reticular nuclei.

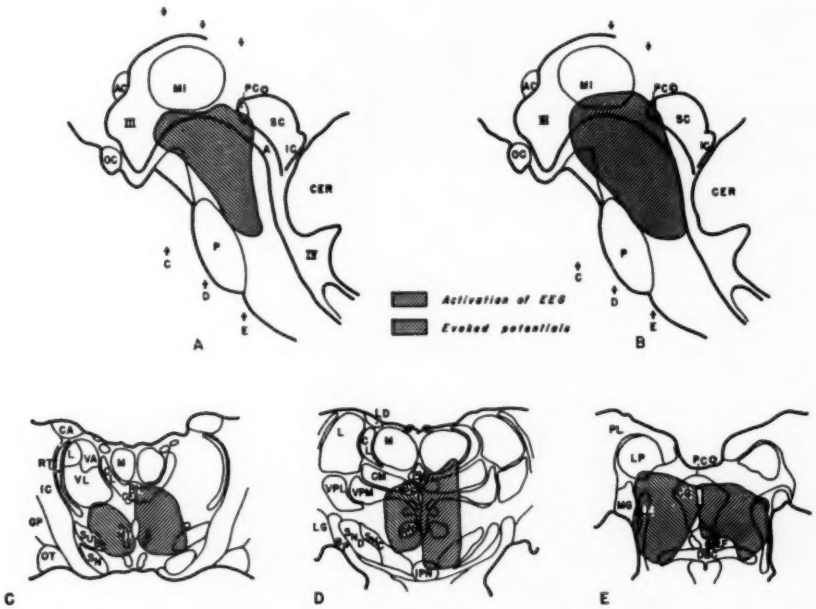

Fig. 3.—Localization of collateral potentials from stimulation of the sciatic, splanchnic, and auditory systems (*B* to *E*) and of the excitable region for production of electrocortical desynchronization (*A*, *C*, *D*, and *E*) is outlined in sagittal view (*A*, *B*) and in transverse sections through the brain stem (*C*, *D*, and *E*) of monkeys 1 through 5. The level of each transverse section is indicated by the arrows on the longitudinal view. Abbreviations used in this Figure and in Figures 4 and 7, are as follows: *A*, aqueduct; *AC*, anterior commissure; *BC*, brachium conjunctivum; *BP*, basis pedunculi; *CA*, caudate nucleus; *CE*, nucleus centralis medialis; *CER*, cerebellum; *CG*, central gray substance; *CL*, nucleus centralis lateralis; *CM*, centrum medianum; *DBC*, decussation, brachium conjunctivum; *GP*, globus pallidus; *IC*, internal capsule; *IPN*, interpeduncular nucleus; *L*, nucleus lateralis; *LD*, nucleus lateralis dorsalis; *LG*, lateral geniculate body; *LL*, lateral lemniscus; *LP*, nucleus lateralis posterior; *M*, nucleus medialis; *MG*, medial geniculate body; *ML*, medial lemniscus; *MT*, mamillothalamic tract; *OT*, optic tract; *PC*, nucleus paracentralis; *PCO*, posterior commissure; *PL*, pulvinar; *PM*, paramedian nucleus; *RH*, rhomboid nucleus; *RN*, red nucleus; *RT*, reticular nucleus; *SNC*, substantia nigra (compacta); *SND*, substantia nigra (diffusa); *SUB*, subthalamic nucleus; *TEG*, tegmentum; *VA*, nucleus ventralis anterior; *VPL*, ventroposterolateral nucleus; *VPM*, ventroposteromedial nucleus; *Z*, zona incerta; *III*, third ventricle; *IV*, trochlear nerve.

Throughout the areas outlined, all potentials were essentially similar, appearing as spike or spike-and-wave discharges (Figs. 1 and 2). The recorded responses, whether from visual, visceral, auditory, or somatic stimuli, appeared the same throughout the activating region, although the form of response was never stereotyped.

Repetitive stimulation of the sciatic and sympathetic nerves (5 volts, 100 per second, 1 msec.) produced a pronounced increase in rate in the normally fast back-

Fig. 4.—Localization of collateral potentials from stimulation of the optic nerve is outlined in sagittal view (*A*) and in transverse sections (*B*, *C*, and *D*), made at the levels of arrows in *A*.

ground activity of the central core of the brain stem, throughout the extent of the area from which evoked potentials were recorded, which change in the brain stem was associated with desynchronization of electrocortical activity (Fig. 5*B*). Such increase in background activity persisted for many seconds after cessation of the stimulus and correlated with a prolongation of cortical desynchronization. Similar stimulation of the medial lemniscus produced the same cortical desynchronization (Fig. 5 *C*). Such alteration of electrical activity was not observed after repetitive aural stimulation (alarm clock), and direct excitation of the cochlear nerve was not attempted.

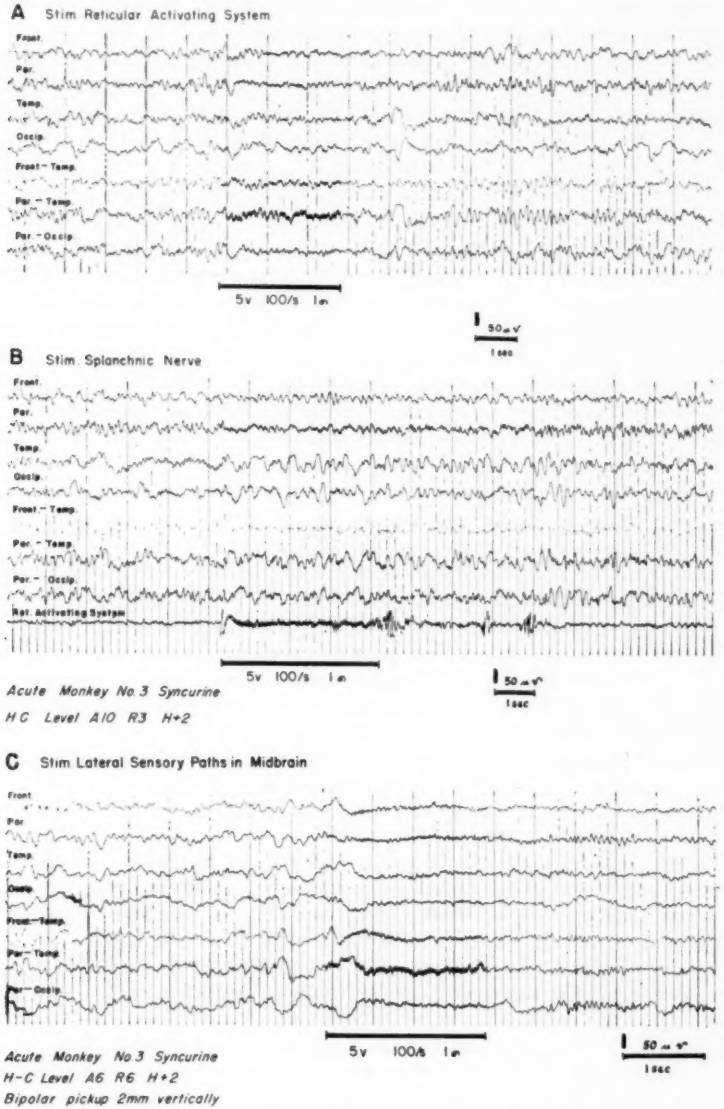

Fig. 5.—Repetitive stimulation of the splanchnic nerve causes the same desynchronization of electrocortical activity (*B*) as does similar stimulation of the reticular activating system (*A*). Increase in fast activity in the reticular activating system itself is seen to coincide with the cortical effect (*B*). This same activation was seen on stimulation of later central sensory pathways as far forward as the midbrain (*C*).

When repetitive stimulation was applied to the central core of the brain stem, a pronounced desynchronizing influence upon electrocortical activity was demonstrated (Figs. 5 *A* and 6). This cortical activation was most pronounced when the prestimulus tracing showed synchronous slow activity characteristic of a sleeping record (Fig. 6, upper right), but even when the electrocorticogram was moderately alerted, activation could still be discerned, though it was less conspicuous (Fig. 6, upper left). In the drowsing electroencephalogram such induced activation persisted long after cessation of the stimulus and was associated with evidence of behavioral arousal in the animal at times when it was capable of moving (Fig. 6, middle and lower tracings).

As seen in Figure 3, the region from which such activation could be incited corresponded closely to the region from which collateral afferent discharge was earlier noted to be recorded. Stimulation in the region of the thalamus produced cortical desynchrony somewhat less regularly than similar excitation in the tegmentum, but electroencephalographic arousal was fairly commonly seen during and after excitation of portions of the centrum medianum, reticular nucleus, and nucleus ventralis anterior. Frequently a cortical recruiting response to 10-per-second stimulation and desynchronization to 100-per-second excitation were obtained from the same point, but in general recruitment was observed from areas farther dorsally situated, where more rapid stimulation did not alter electrical activity of the cortex. In two animals, cortical activation occurred after stimulation of isolated areas in the paracentral and lateral nuclei of the thalamus, but here the resulting desynchronization was not generalized and was of short duration.

Alteration of electrocortical activity on stimulation of the midbrain system was not always uniform over the cortex, frequently showing up in some areas and not in others. On stimulation of the sciatic or splanchnic nerve, cortical activation was usually limited to the frontal and parietal cortex, being most apparent in the primary receptive area. Direct stimulation of the central-brain-stem system resulted in alteration of electrocortical activity most frequently in the frontal and parietal regions, somewhat less constantly in the temporal area, and least commonly in the occipital cortex. Also, in the temporal and occipital regions, the electrocorticogram returned more rapidly to normal after cessation of the stimulus. This gradation of response was always present, and localized activation of the temporal and occipital regions was never observed. Furthermore, there was no correlation between the site of stimulation in the activating system and the area of cortical response. It seemed, rather, that the more excitable areas in the brain stem exerted a diffuse cortical response, and the less active regions a more frontally oriented local response, wherever the stimulus was applied throughout the rostrocaudal extent of the excitation core. As previously noted, cortical activation was clearest and most prolonged when the prestimulus cortical tracing was characterized by high-voltage slow waves, but the response did not appear to depend upon any particular preexisting condition of cortical activity.

While such activation of the electrocorticogram was the commonest response observed on stimulation of the reticular activating system, a synchronous discharge of 20- to 40-per-second waves occurred in the cortex after excitation of certain points in the cephalic half of the central tegmental core with the same stimulus, which in other areas resulted in desynchrony (Fig. 7). Stimulation points from which such

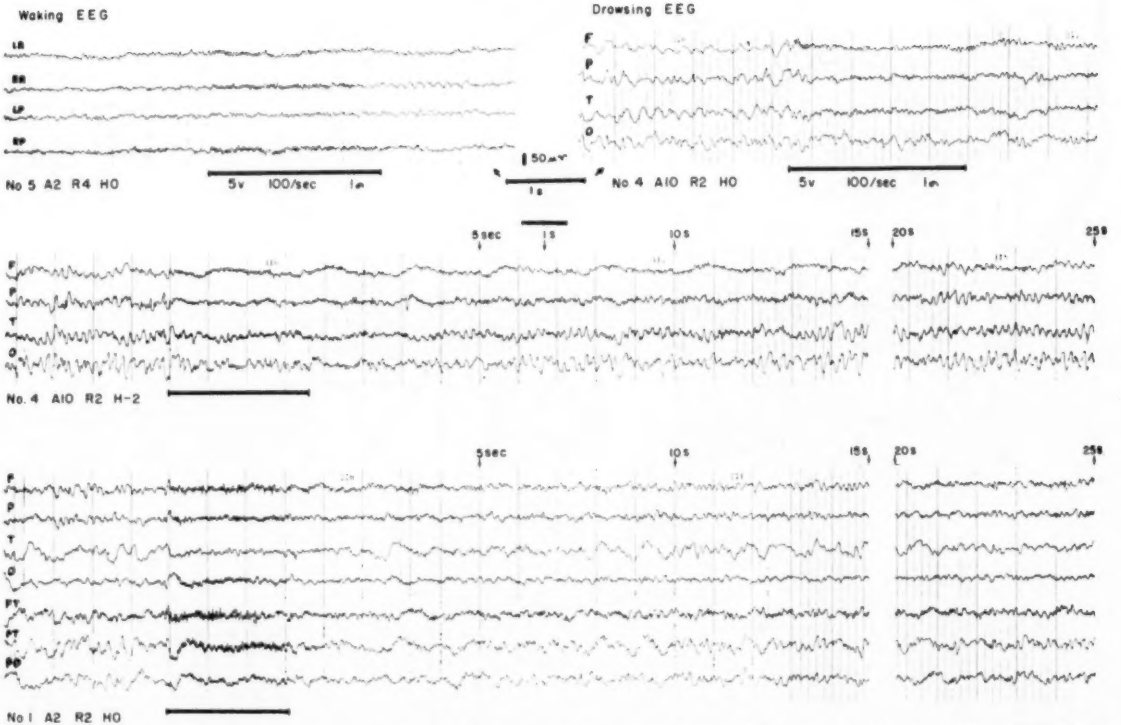

Fig. 6.—The effect on the electrocortical tracing of stimulation of the reticular activating system is shown in the waking tracing (upper left) and drowsing tracing (upper right). In the latter situation activation of the electroencephalogram persists for a prolonged interval (two lower tracings) and is frequently associated with behavioral arousal of the animal. Abbreviations are as follows: *F*, frontal; *FT*, frontotemporal; *LA*, left anterior; *LP*, left posterior; *O*, occipital; *P*, parietal; *PO*, parieto-occipital; *PT*, parietotemporal; *RA*, right anterior; *RP*, right posterior, *T*, temporal.

Fig. 7.—The cross-section diagram on the right shows the settings of the stimulating electrode on one complete puncture through the activating system of the midbrain. Corresponding cortical tracings for each setting are shown on the left. Prominent electrocortical activation in the form of 40 and 20 cps discharges first appeared in the frontal leads at H + 2, spread to all leads as the electrode was advanced, and disappeared below H — 2.

cortical response was elicited were confined to the cephalic portion of the tegmentum, and were rarely encountered ahead of or behind it. In one animal such rapid synchrony resulted from stimulation of the activating system as far laterally as the medial lemniscus, but never was observed after excitation of peripheral nerves. Frequently, the response occurred on stimulation of several adjacent points, but occasionally resulted from excitation of a single area surrounded by placements from which desynchrony was effected. The cortical wave pattern persisted only for the duration of the stimulus, being replaced thereafter by a return to the prestimulus tracing or to desynchronization, which was usually not as prolonged as that occurring after simple activation of the electroencephalogram.

Both desynchronization of the electroencephalogram and the 20- to 40-per-second wave pattern resulting from stimulation of suitable areas in the activating system were observed with stimulating frequencies of from 25 to 300 per second, but the responses were optimum when the repetitive stimuli were delivered at the rate of 100 per second. Occasionally, on stimulation of the cephalic end of the system described, recruiting waves could be induced in the cortex with 10-per-second stimulation, but in general the cerebral surface did not respond to such frequencies delivered to the central core. The electrocorticogram was never altered by the use of lower stimulating frequencies delivered to this excitation area, nor could evoked potentials be recorded in the cortex by single-shock stimuli delivered to it.

COMMENT

The results reported indicate the presence of a medially situated activating system in the brain stem of the monkey, corresponding to that already known to exist in the cat.[5] This system has been shown to receive throughout its extent impulses from visual and visceral systems, as well as impulses mediated by proved collateral fibers from the long auditory and somatic sensory pathways. Collaterals from the latter two systems have been found to enter the central core of the brain stem throughout its longitudinal extent from the medial and lateral lemnisci as far cephalad as the respective thalamic relay nuclei.[3] Studies have not been completed on visual and visceral collaterals, although presumably they leave their prethalamic pathways to enter the activating system in the same manner as do auditory and somatic collaterals. Recent description of a splanchnic relay in the ventroposterolateral nucleus of the thalamus,[6] in particular, would suggest an anatomical and physiological parallel of visceral and of somatic afferent collaterals to the reticular formation. The absence of evoked potentials of vagus origin is difficult to explain. Bailey and Bremer [7] have described localized cortical activation from vagal stimulation similar to that from stimulation of other peripheral sources, and further search will be necessary to identify the collateral participation of impulses from this source in the brain-stem system.

That the medially situated area of the brain stem subserves a specialized function, rather than that simply of relay or conduction, is suggested by a study of its

5. Starzl, Taylor, and Magoun.[3] Moruzzi and Magoun.[4]

6. Patton, H. D., and Amassian, V. E.: Thalamic Relay of Splanchnic Afferent Fibers, Am. J. Physiol. **167**:815-816, 1951.

7. Bailey, P., and Bremer, F.: A Sensory Cortical Representation of the Vagus Nerve, with Note on Effects of Low Blood Pressure on Cortical Electrogram, J. Neurophysiol. **1**:405-412 (Sept.) 1938.

afferent connections. Single-shock-evoked potentials recorded in the area from peripheral stimulation clearly indicate that collaterals from each of the four systems studied pervade the entire central core. There is no organization of the area whatever with regard to the segregation of incoming fibers into discrete sensory modalities, all systems feeding into it diffusely throughout its extent. Moreover, such potentials recorded in the central core are seen to attenuate when evoked from repetitive stimulation to a single source and to interact when evoked from temporally approximating stimuli to two different sources.

The two latter phenomena suggest the presence in the central core of the brain stem of a common system of neurons with multiple relays which are discharged equivalently by all modalities of afferent stimulation. Such a system would not appear, therefore, to be involved in the conscious perception of one modality of sensation as distinct from another. Rather, it would seem to be involved in such afferent functions as are common to each and every type of sensation, as, for example, the attraction of attention. It may further be proposed that sensory impulses ascending through the brain stem induce through the central activating system an alert or attentive state in the cortex, rendering it capable of conscious perception of the discharge carried to primary receptive areas over the classic sensory paths.

Further support for the proposal may be derived from observations on the effect of repetitive stimuli to peripheral nerves or classic sensory paths in the brain stem. Repetitive stimuli delivered at the rate of 100 per second to the sciatic or splanchnic nerves were capable of exciting the entire central core of the brain stem to activity. Such activation of the area by peripheral sensory stimulation was associated with a simultaneous desynchronization of electrocortical activity, the discharge in both regions persisting long after cessation of the stimulus. The identical effect was observed on stimulation of the medial lemniscus, and previous studies in the cat have indicated that activation of the central core of the brain stem and of the cortex persists after destruction of the cephalic end of the sensory lemnisci or of their relay nuclei.[8] It is clear, therefore, that sensory stimulation is capable of simultaneously exciting the tegmentothalamic area of collateralization and the cerebral cortex. Additional information indicates that such cortical desynchronization on peripheral stimulation, characteristic of the change of the electroencephalogram from drowsing to wakefulness, is mediated through this central tegmentothalamic core, or, as it seems justifiable to call it, the activating system.

This area of collateralization receiving such a profusion of sensory stimuli and capable of activation by them extends at least from the lower border of the pons, caudally, to the ventromedial thalamus, cephalically. It is coexistent, therefore, with the facilitatory area of Rhines and Magoun [9] and superiorly with the diffuse thalamic projection system of Dempsey and Morrison.[10] It would not seem entirely fortuitous, therefore, that cerebral function involving the activating system described, that of association elaborated by the diffuse thalamic projection nuclei and of facilitation

8. Starzl, T. E.; Taylor, C. W., and Magoun, H. W.: Ascending Conduction in the Reticular Activating System with Special Reference to the Diencephalon, J. Neurophysiol. **14**:461-477 (Nov.) 1951.

9. Rhines, R., and Magoun, H. W.: Brain Stem Facilitation of Cortical Motor Response, J. Neurophysiol. **9**:219-229 (May) 1946.

10. Dempsey, E. W., and Morrison, R. S.: Production of Rhythmically Recurrent Cortical Potentials After Localized Thalamic Stimulation, Am. J. Physiol. **135**:293-300 (Jan.) 1942.

of lower motor outflows, dependent upon reticulospinal connection, should all be set into play simultaneously by peripheral stimuli and mediated by an interrelated area in the brain stem.

Direct excitation of the activating system with a stimulus identical to that which effected its discharge on peripheral-nerve stimulation resulted usually in the same cortical desynchronization. The electrocortical and, when the preparation was suitable, the behavioral arousal was unmistakable and occurred in identical fashion wherever the activating system was stimulated. Thus, stimulation at the posterior end of the system resulted in essentially the same cortical activation as did stimulation in the anterior end, a characteristic which further suggests its unified function. The prolongation of such cortical desynchronization after the cessation of the stimulus to the central core strongly indicates that threshold activation of the medial region excites it to sustained spontaneous discharge, which mediates the persisting "arousal" in the cortex.

The pathways by which impulses from the reticular activating system reach the cortex are not entirely clear. Multineuronal rostral conduction of impulses in the activating system and to the diffuse thalamic projection nuclei [8] have been described. Previous experiments on the cat have suggested that probably both thalamic and capsular corticipetal routes were thence involved.[8] That such is probably the case is suggested by the fact that activation was occasionally effected by stimulation in the medial and lateral thalamic nuclei at some distance from the main body of active core. Furthermore, cortical excitation was also rarely observed when the stimulating electrode was laterally situated in the internal capsule. Bilaterality of cortical response was frequently observed.

The tendency toward rostral orientation of the cortical response to stimulation of the activating system has been noted before in the cat.[11] This tendency appears to be even more prominent in the monkey, as activation was relatively rarely seen in the occipital lobes, and then only when the entire cortex was involved. Conversely, stimulation of progressively less active areas in the central core resulted in disappearance of cortical effect in the occipital and temporal regions. The effect was always present in the rostral half of the cortical convexities and, while uniformly seen in the frontal lobe, was frequently most clear-cut over the anterior parietal region.

Such rostral orientation of corticipetal system traversing this central core is hardly novel in mammals of higher order. The motor pallidothalamocortical [12] and superior cerebellar radiations and the autonomic radiations to the frontal lobes from the hypothalamus are so oriented. Moreover, the diffuse thalamic projection nuclei have recently been shown to communicate predominantly with anterior cortical areas.[13] It might be logical to expect frontal orientation, therefore, of the activating system because of its close anatomical, and probably functional, relationship with the diffuse thalamic projection nuclei.

Destructive lesions of the activating system in cats have produced profoundly comatose animals, the synchronous electrocortical activity characteristic of such a

11. Moruzzi and Magoun.[4] Starzl, Taylor, and Magoun.[8]

12. Papez, J. W.: A Summary of Fiber Connections of the Basal Ganglia with Each Other and with Other Portions of the Brain, A. Res. Nerv. & Ment. Dis., Proc. (1940) **21**:21-68, 1942.

13. Starzl, T. E., and Whitlock, D. G.: The Diffuse Thalamic Projection System in the Monkey, J. Neurophysiol., to be published.

state responding feebly to desynchronizing stimulation.[14] The question might possibly be raised as to whether or not the laconic postlobotomy state in man, together with prolonged slow-wave activity in the frontal lobes,[15] may be the result of isolation of a large area of cortex from the activation system with which it most intensely connects.[15]

SUMMARY

Evidence is presented which indicates that there exists in the monkey, as in the cat, a centrally located area comprising the midbrain tegmentum, the subthalamus and hypothalamus, and the medial portion of the thalamus in which evoked potentials can be recorded from peripheral stimuli delivered to the somatic, visual, auditory, and visceral systems. Such potentials are similar to those evoked in the lateral sensory pathways but differ in that they attenuate when rapidly evoked from stimulation of a single sensory nerve and interact when the eliciting shocks are delivered in close approximation to two different sources.

Rapidly repetitive stimuli delivered to the cut sciatic or splanchnic nerves or to the lateral sensory pathways in the brain stem cause an increase in the normally fast background activity throughout the activating system and a simultaneous desynchronization of electrocortical activity. The same cortical desynchronization occurs on high-frequency stimulation anywhere in the reticular activating system and usually persists long after cessation of the stimulus. There is a tendency for such electrocortical activation to be frontally oriented, but it can be observed over the entire hemisphere on stimulation of the most excitable areas in the central core.

The results of these experiments indicate that this centrally situated area in the brain stem, functioning as a unit, is subject to excitation by peripheral sensory stimulation. Such excitation effects electrical activation of the cortex and behavioral arousal of the animal. The evidence suggests that this medially mediated mechanism plays an important role in such physiological reactions to sensory stimuli as awareness of sensation, arousal to wakefulness, or alerting to attention.

14. Lindsley, D. B.; Schreiner, L. H.; Knowles, W. B., and Magoun, H. W.: Behavioral and EEG Changes Following Chronic Brain Stem Lesions in the Cat, Electroencephalog. & Clin. Neurophysiol. **2**:483-498 (Nov.) 1950.

15. Levin, S.; Greenblatt, M.; Healey, M. M., and Solomon, H. C.: Electroencephalographic and Clinical Effect of Prefrontal Lobotomy with Consideration of Postlobotomy Convulsive Seizures, in Greenblatt, M.; Arnot, R., and Solomon, H. C.: Studies in Lobotomy, New York, Grune & Stratton, Inc., 1950, pp. 400-427.

EFFECTS OF CHRONIC LESIONS IN CENTRAL CEPHALIC BRAIN STEM OF MONKEYS

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THERE has been shown to exist in the median cephalic portion of the brain stem of cats [1] and monkeys [2] an area comprising the midbrain tegmentum, the subthalamus and hypothalamus and the medial portion of the thalamus which subserves a specialized function in the response of the animal to sensory stimuli. This area can be readily excited by peripheral stimulation, such excitation, or that produced by direct stimulation with a probing electrode, arousing the sleeping animal to wakefulness and altering its electroencephalogram in a manner consistent with such a change. The evidence suggests that this activating system is of particular importance in initiating and maintaining an alert or attentive state in the animal, rendering it capable of reacting adaptively to stimuli in a way impossible in sleep.

Lindsley and associates [3] have observed that lesions placed so as to destroy a significant portion of this area in cats were followed by chronic somnolence and electroencephalographic synchrony in the animals. The present study was undertaken to determine the effect of similar lesions on behavioral and electrocortical activity in monkeys. It was found that the animals so prepared were even more profoundly unresponsive, and showed even greater disturbance in their electrocorti-

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Reviewed in the Veterans Administration Hospital and published with the approval of the Chief Medical Director. The statements and conclusions published by the authors are the result of their own study and do not necessarily reflect the opinion or policy of the Veterans Administration.

1. (*a*) Moruzzi, G., and Magoun, H. W.: Brain Stem Reticular Formation and Activation of the EEG, Electroencephalog. & Clin. Neurophysiol. **1**:455-473 (Nov.) 1949. (*b*) Starzl, T. E.; Taylor, C. W., and Magoun, H. W.: Collateral Afferent Excitation of Reticular Formation of Brain Stem, J. Neurophysiol. **14**:479-496 (Nov.) 1951; (*c*) Ascending Conduction in Reticular Activating System, with Special Reference to the Diencephalon, ibid. **14**:461-477 (Nov.) 1951.

2. French, J. D.; von Amerongen, F. K., and Magoun, H. W.: An Activating System in the Brain Stem of the Monkey, A. M. A. Arch. Neurol. & Psychiat., this issue.

3. Lindsley, D. B.; Schreiner, L. H.; Knowles, W. B., and Magoun, H. W.: Behavioral and EEG Changes Following Chronic Brain Stem Lesions in the Cat, Electroencephalog. & Clin. Neurophysiol. **2**:483-498 (Nov.) 1950.

cal activity, than was the case in cats. The extension of these observations to animals with a higher degree of encephalization than exists in carnivores emphasizes the potential importance of the area in cerebral function in man.

METHOD AND MATERIAL

Electrolytic lesions were made under sterile precautions in the brain stem of 10 monkeys (Macacus mulattus) anesthetized with pentobarbital sodium. The lesion-making electrode was passed through a small craniotomy opening in the skull vertex and oriented by means of the Horsley-Clarke stereotaxic instrument.

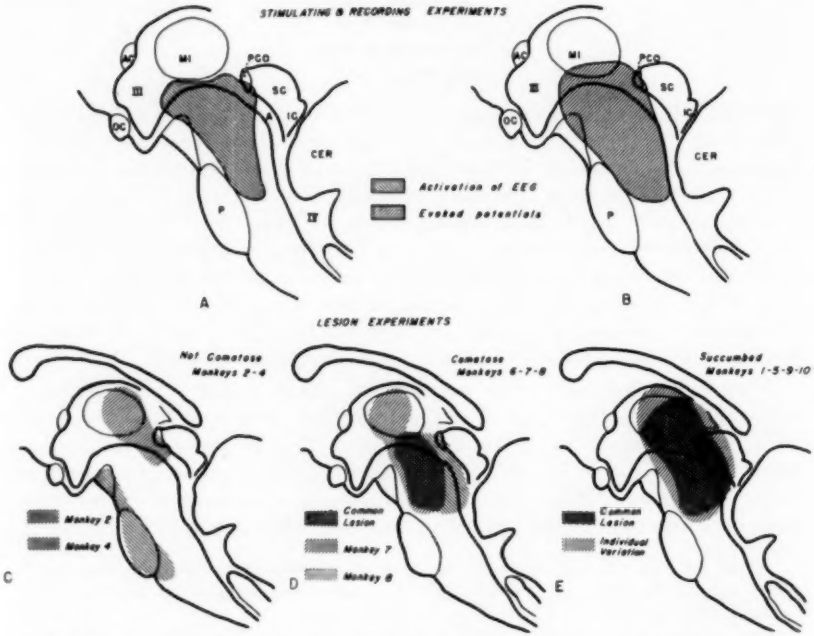

Fig. 1.—Reticular activating system. Midsagittal reconstructions of the brain stem showing (*A*) area from which activation of the electroencephalogram was obtained on direct stimulation, (*B*) area from which evoked potentials were recorded on peripheral stimulation, (*C*) to (*E*) areas destroyed in animals of the present series. The data presented in *A* and *B* are from previous experiments.[2]

Abbreviations used in Figures 1 and 2 are as follows: Thalamic nuclei, *AV, CL, CM, H, LA, LD, LG, LP, M, MG, PC, PL, RT, RH, VL, VM, VPL, VPM*; iter, *A*; anterior commissure, *AC*; basilar artery, *BA*; basis pedunculi, *BP*; caudate nucleus, *CA*; cerebellum, *CER*; foramen caecum, *FC*; inferior colliculus, *IC*; interpeduncular nucleus, *IPN*; lateral lemniscus, *LL*; massa intermedia, *MI*; medial lemniscus, *ML*; optic chiasm, *OC*; pons, *P*; posterior commissure, *PCO*; red nucleus, *RN*; subthalamic nucleus, *SUB*; superior colliculus, *SC*; substantia nigra, *SN*; third ventricle, *III* (third nerve nucleus, Fig. 2); fourth ventricle, *IV*.

After operation, frequent neurological observations were made and repeated electroencephalograms were recorded with a Grass amplifier and ink-writer through silver disc electrodes applied to the scalp. Tracings were made in the sleeping and, when the animal was behaviorly responsive, the waking state. In all cases, however, vigorous sensory stimuli were interjected in the form of clicks, whistles, and claps to the auditory system and pinches to

the somatic system in an effort to arouse the animal and activate the electroencephalogram. Terminal experiments were performed on certain animals to verify the integrity of the long projection systems in which appropriate movements were observed on stimulation of Area 4 and evoked potentials were recorded in primary sensory areas after suitable peripheral stimulation. The brains were sectioned serially at the completion of each experiment and the exact extents of the lesions determined.

RESULTS

One animal subjected to the same procedures as the rest except for the production of lesions showed no behavioral or electroencephalographic alterations. Of the remaining nine animals, four succumbed during the first day after operation without

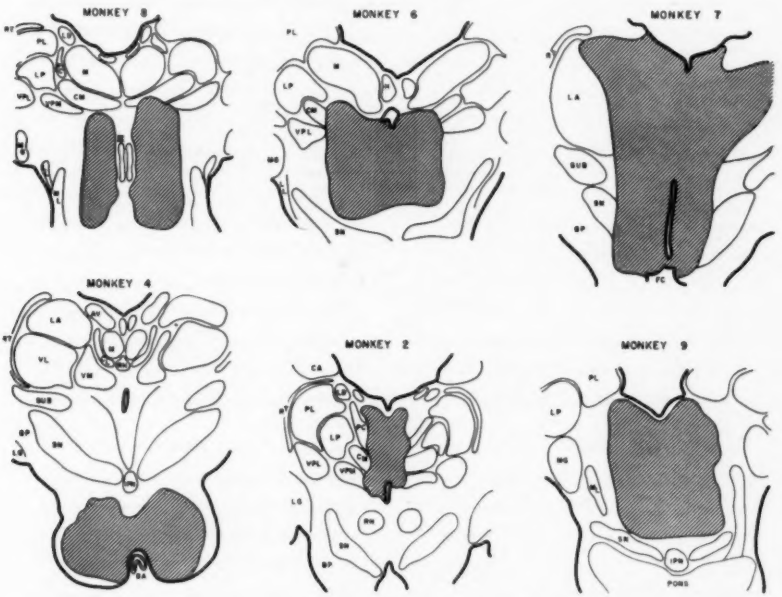

Fig. 2.—Diagrams of cross sections showing extent of lesions (shaded areas) in the reticular activating system in all animals at point of greatest magnitude. Monkey 9 is representative of Monkeys 1, 5, and 10. Note that the activating system is involved in Monkeys 6, 7, 8, and 9, but not in Monkeys 2 and 4.

exhibiting behavioral response and before electroencephalograms could be recorded. The lesions in these animals were essentially similar in extent, being the most extensive in the series (Figs. 1 *E* and 2, Monkey 9). In each case practically the entire central portion of the brain stem was destroyed, including the major part of the tegmentum and the basal tectum cephalad from the midpontine area to, and including most of, the medial thalamus. Spared, however, were the lateral sensory and motor projection pathways.

One animal (Monkey 2) responded promptly after the operation and, except for being somewhat more subdued and tractable than before, moved, ate, slept, and

wakened normally. On the seventh postoperative day, the electroencephalogram still showed slightly slower activity than normal, but was markedly affected by afferent stimulation. The response (Fig. 3*A*) took the form of high voltage, 10/cps waves, rather than the commoner desynchronization of slow activity. In earlier stimulation experiments[2] similar responses have been observed on direct, high-frequency excitation of portions of the cephalic midbrain tegmentum. After 25 days, relatively normal sleeping and waking tracings were obtained (Fig. 3).

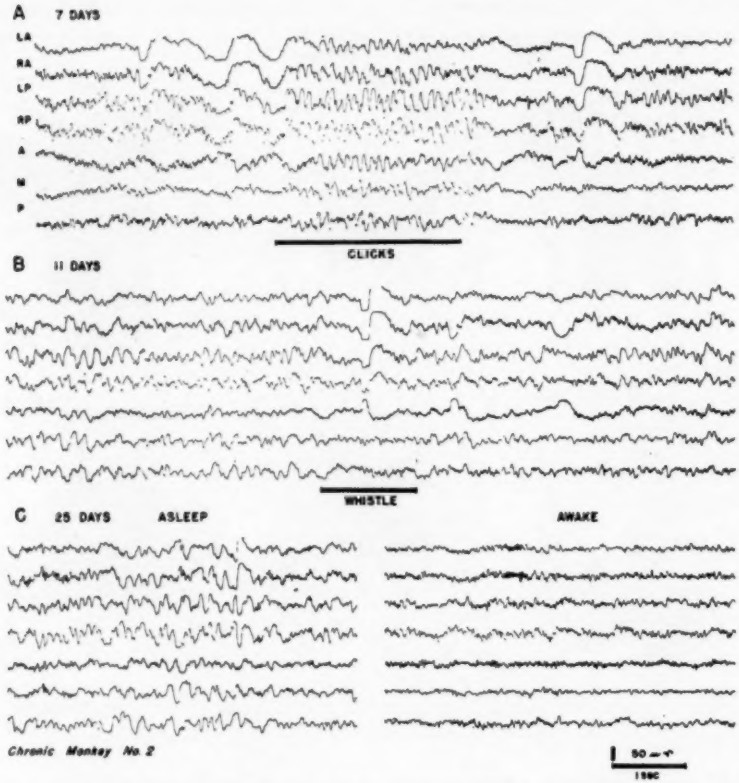

Fig. 3.—Serial electroencephalographic tracings for Monkey 2, in which the lesion did not involve the tegmentum, illustrating electrocortical response to afferent stimuli. Note activation on auditory stimulation as early as 7 days (*A*), with persistent desynchronization at 11 days (*B*). Relatively normal waking and sleeping tracings are recorded at 25 days (*C*).

At autopsy, after 49 days, the lesion, smaller and more dorsally situated than others in the series, was found to involve the posterior medial part of the thalamus and only a very small portion of the anterior periaqueductal region (Fig. 2). Almost the entire tegmentum was spared.

Monkey 4 was quite helpless after operation and was thought initially to be comatose; yet on the second day he was observed to open his eyes. Subsequently,

it was noted that, while he could not move purposefully, hypertonus, reflex withdrawal of extremities, reflex grasping, occasional vocalization, and increase in deep reflexes were present. The subsequent postoperative course was characterized by

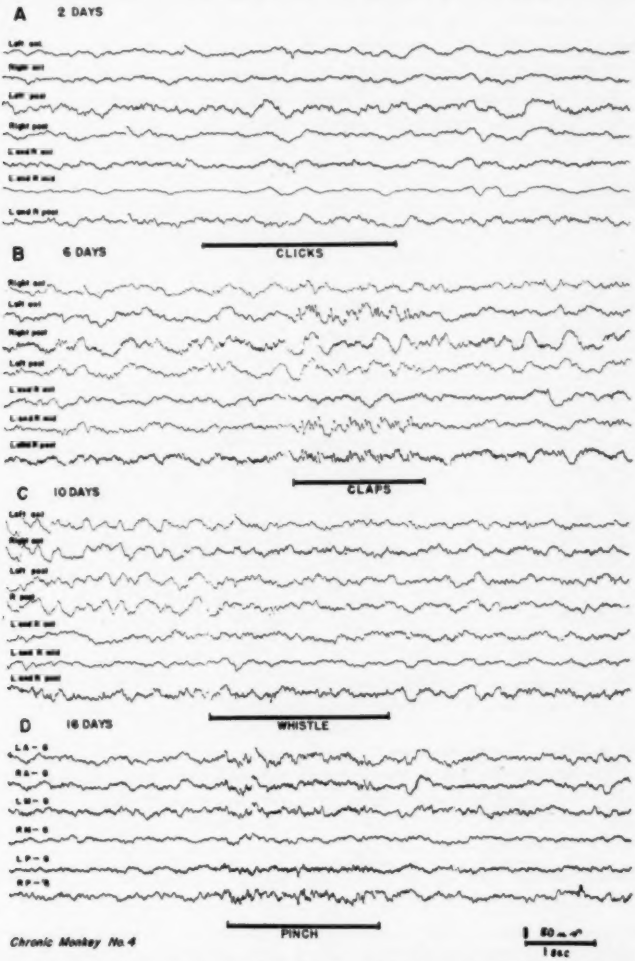

Fig. 4.—Serial electroencephalographic tracings on Monkey 4, in which the lesion was below the activating system. Note activation at six days (*B*) and persistent desynchronization at 10 days (*C*) on auditory stimulation. All tracings were less synchronous than in the animals with lesions involving the midbrain tegmentum (Figs. 5, 7, and 9).

the continued immobility of the animal and by gradually increasing periods of what appeared to be normal wakefulness. Death occurred on the 23d day of intercurrent infection. An electroencephalogram on the second day showed more slow activity

than normal, but was far less synchronous than that observed in other truly comatose animals (Fig. 4 *A*). On the sixth day even more normal fast activity was present, and at this time desynchronization of the tracing on sensory stimulation could be clearly demonstrated (Fig. 4 *B*). Similar electrocortical activation could be observed

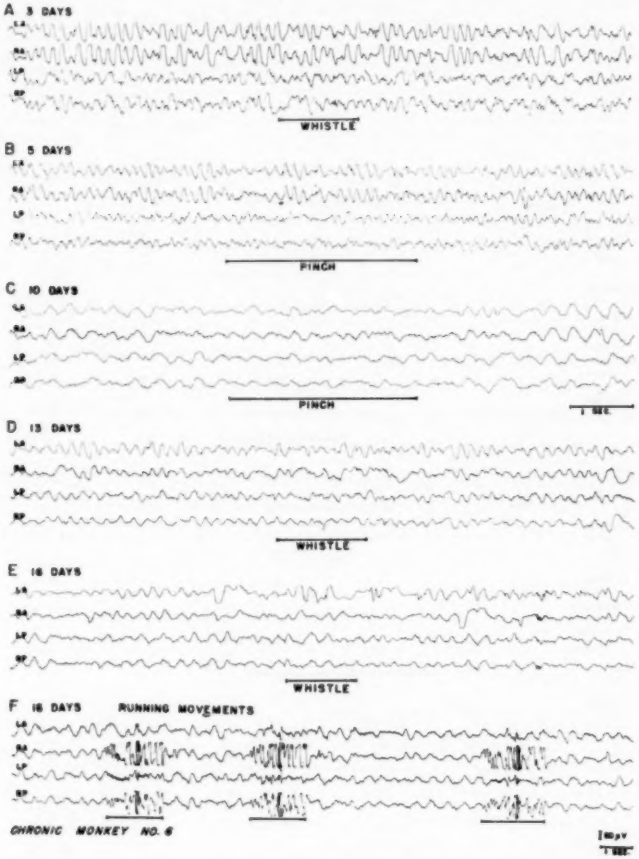

Fig. 5.—Electroencephalographic recordings from Monkey 6, in which the lesion involved a major portion of the reticular activating system. Note persistent synchrony in all tracings, absence of activation on peripheral stimulation, and failure of improvement in tracings throughout the survival period. In *F*, the artifact produced by spontaneous running movements is not associated with desynchronization of the record, suggesting that such movements did not depend on electroencephalographic arousal.

thereafter during the survival period, particularly if the animal was stimulated when the electroencephalogram showed slow activity characteristic of sleep (Fig. 4 *C, D*). At such times desynchronization persisted long after cessation of the stimulus (Fig.

4 *C*). At autopsy, after 23 days, the lesion was found to be confined to the basis pedunculi and basis pontis, the tegmentum [4] being grossly spared (Figs. 1 *C* and 2, Monkey 4).

The remaining three animals had similar postoperative courses and appeared to be comatose most of the time. Monkey 6 was the most motile of the three, it being possible to arouse him occasionally to short periods of activity, characterized by running movements of the extremities, blinking of the eyes, and occasionally vocal chirruping. Such behavioral arousal was occasionally spontaneous, or even cyclic; but movement was never purposefully adaptive and the animal was at all times

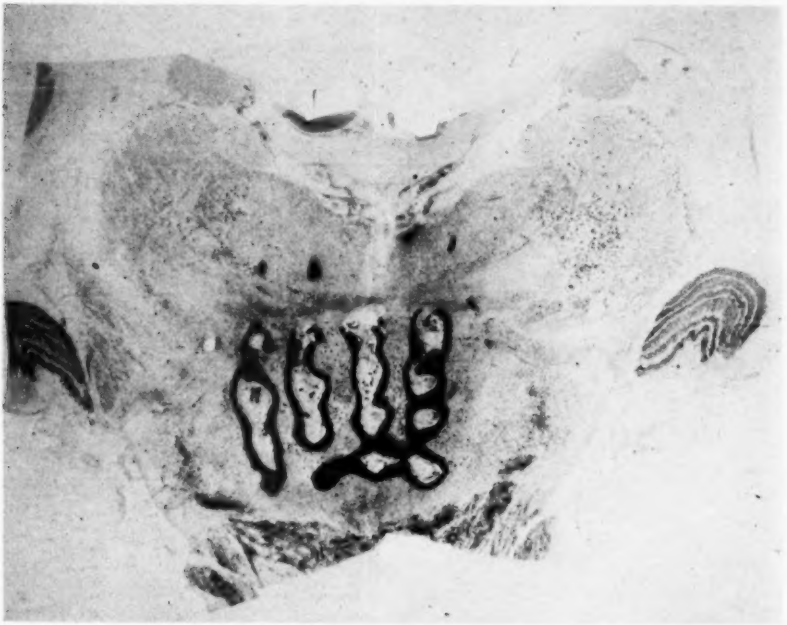

Fig. 6.—Transverse section through greatest extent of lesion in cephalic portion of tegmentum in Monkey 6. Thionine stain.

completely helpless, requiring tube feeding and complete nursing care. The electroencephalogram of this animal was essentially a stupor tracing throughout the 18-day survival period (Fig. 5). The artifact in the record coincident with running movements was not preceded by any change in the tracing and was followed immediately by resumption of a pattern identical with that present before (Fig. 5 *F*). On only one occasion, 13 days after operation, was it possible to see a slight semblance of activation of the electroencephalogram on sensory stimulation, but this desynchro-

4. Microscopically, however, the cells of the tegmental area were fewer than normal and frequently stained poorly. Such alteration appeared to stem from relative anoxemia, resulting from narrowing of the basilar artery, which was partially enclosed by the lesion and surrounded by adhesions.

nization lasted only for the duration of the stimulus. At no other time during the 18-day survival period was similar activation possible.

Monkey 7 was completely comatose and akinetic for four days after operation, after which time he would open his eyes and move purposelessly a little and then promptly go back to sleep. After seven days, however, the animal was no longer responsive to painful stimuli, and he died 12 days after operation. Throughout the

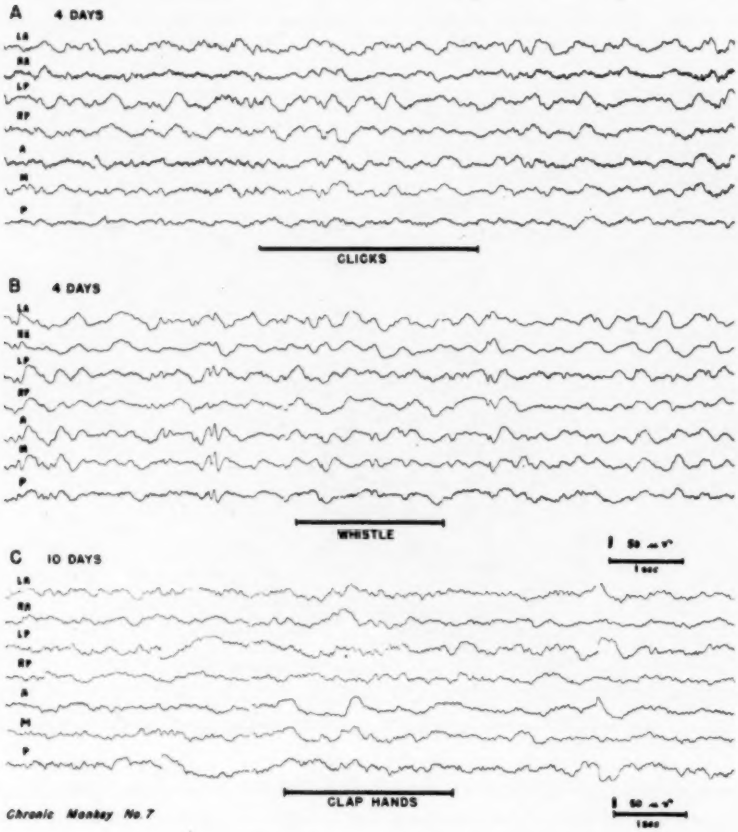

Fig. 7.—Serial electroencephalographic tracings in Monkey 7. As in Monkey 6, the tracing remained hypersynchronous permanently, owing to destruction of a major portion of the activating system. Correspondingly, the animal showed no evidence of behavioral arousal on peripheral stimulation.

survival period, the electroencephalogram was characterized by continuous slow-wave activity, which could never be desynchronized by sensory stimuli (Fig. 7).

Monkey 8 was completely comatose and akinetic for 10 days after operation (Figs. 8 and 9), after which time he would briefly open his eyes and move his extremities purposelessly a little. Subsequently, however, his periods of apparent

alertness increased somewhat in frequency and duration. During these periods he would occasionally raise his head and vocalize, and would chew and swallow small bits of food placed in his mouth. The electroencephalogram was again characterized by continuous slow-wave activity, but not to the degree seen in Monkeys 6 and 7 (Fig. 9). On only two occasions, however, was any semblance of activation of the record seen on sensory stimulation (Fig. 9 *B* and *D*), and then the desynchronization lasted only for the duration of the stimulus. At 17 days there was a difference

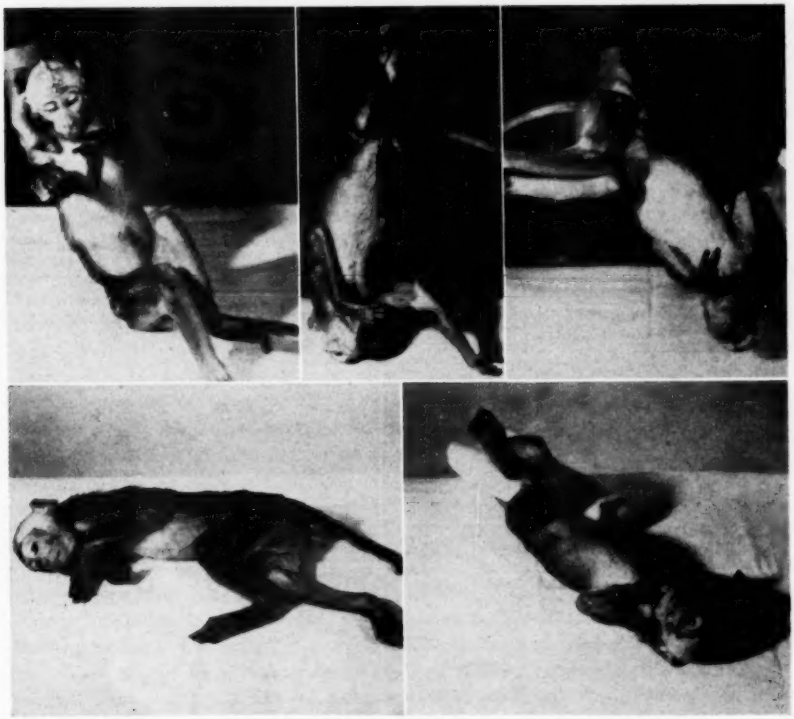

Fig. 8.—Photographs of Monkey 8 made six days after operation. The complete akinesis and, apparently, coma of the animal at this period are illustrated.

between the tracings in what were considered to be the "awake" and the "asleep" states of the animal. The "asleep" tracing showed excessive slow-wave activity, whereas the "awake" tracing showed some desynchronization, although an artifact due to continuous "tensing" at such a time obscured the basic characteristics of the electroencephalogram. At terminal operation on Monkey 8 motor movement was easily effected by stimulating Area 4, and evoked potentials could be recorded in the visual, auditory, and somatic receptive areas on appropriate stimulation, indicating that the long motor and sensory systems were not disturbed.

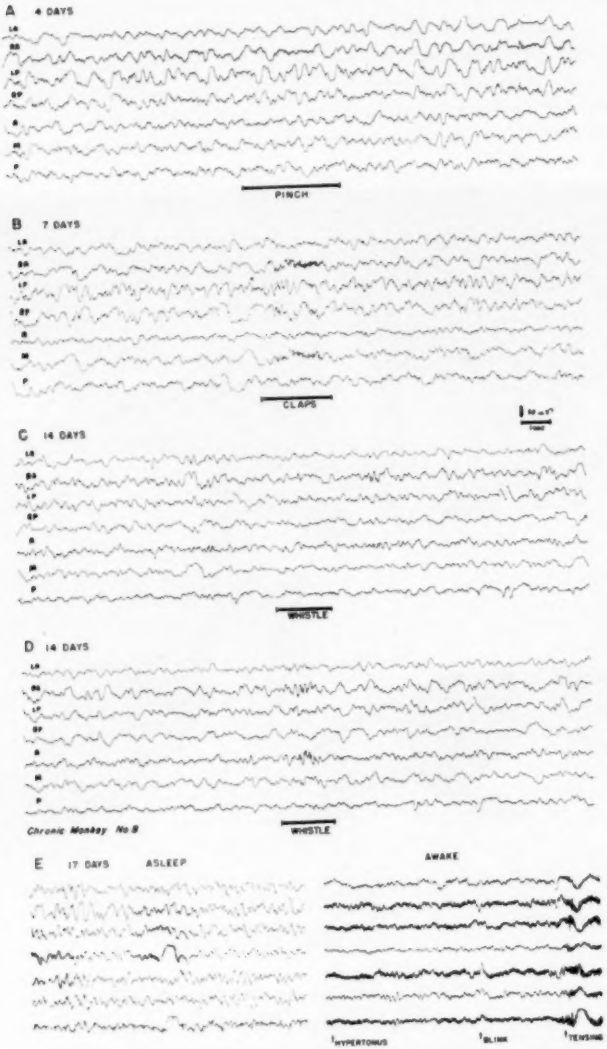

Fig. 9.—Serial electroencephalograms of Monkey 8. All records are characterized by hypersynchrony, although some progressive improvement was noted, culminating in a relatively distinct difference at 17 days between the "asleep" and the "awake" tracing (*E*). It was possible also to see some momentary activation of the record at 7 (*B*) and 14 days (*D*) on peripheral stimulation. The lesions in this animal less completely destroyed the activating system than did those in Monkeys 6 and 7.

The lesions observed at autopsy in Monkeys 6, 7, and 8 were similar in that the main body of destruction in all three animals involved the reticular formation of the tegmentum and the posterior inferior portion of the medial thalamus (Figs. 1 *D*, 2, and 6). Monkey 7 showed, in addition, a thromboischemic area involving a major portion of the medial thalamus, which had apparently occurred about the fourth day after operation and which coincided with an increase in the apparent coma observed in the animal. The lesion in Monkey 8 was the least complete of the three, there being a narrow zone of relatively normal tissue between two lateral areas of destruction (Fig. 2). It is noteworthy that this animal showed less behavioral and electroencephalographic disturbance than the other two, although such changes were still pronounced.

In summary, 7 of 10 animals had lesions involving the cephalic portion of the brain stem in an area previously shown to comprise the reticular activating system. In four animals the area was destroyed practically in its entirety, and none of these animals survived longer than one day.

Cerebral edema occurred in two animals who succumbed (Monkeys 5 and 9) and in three who survived (Monkeys 2, 4, and 6), so that it was not considered a primary cause of death.

The remaining three monkeys, who had less complete destruction of the same area, displayed a postoperative course characterized by hypersomnolence and hypokinesis, with synchronous electroencephalograms incapable of activation by peripheral sensory stimuli. Complications in one animal made it possible to observe the effect on behavioral responsiveness of additional destruction of the area, due to the advent of a vascular occlusion involving the medial thalamus four days after the electrolytic lesion had been made. In this case, the monkey became completely comatose, and no desynchronization of his electroencephalogram could be effected.

In two other animals in which the lesions did not involve a major portion of the reticular activating system, the electroencephalograms showed far less synchrony than those seen in animals with tegmental lesions and could be readily activated by sensory stimulation of the animal. One of these monkeys showed little behavioral change resulting from the lesion (Monkey 2, the medial thalamus only being destroyed). The other (Monkey 4) appeared to be essentially completely immobilized by the lesion, which destroyed the peduncles and pons; but he recovered to the point where he was capable of prolonged electrocortical arousal. The third animal showed no behavioral or electroencephalographic changes from the operative procedure, as no lesion was produced.

COMMENT

The evidence indicating that the cephalic portion of the brain stem functions as an activating system capable of desynchronizing the electroencephalogram and arousing a sleeping animal on excitation by afferent impulses from the somatic, visceral, auditory, and visual sensory systems has beeen evaluated in acute cat and monkey experiments.[5] The effect of chronic lesions made in various parts of this system in cats has been studied by Lindsley and associates.[3] They found that destruction of the activating area of the midbrain produced a state of chronic somno-

5. Moruzzi and Magoun.[1a] Starzl, Taylor, and Magoun.[1b,c] French, von Amerongen, and Magoun.[2]

lence and electroencephalographic synchrony, while lesions which spared this central area had no such effect, even though the lateral sensory pathways were involved. The somnolence and electroencephalographic synchrony which developed after the central lesions, while marked, were not absolute, however, some behavioral arousal and electrocortical desynchronization being possible on peripheral stimulation.

The lesions in the activating system of the monkeys produced in this study appeared to affect the behavior and electrocortical activity of the animal even more drastically than did those of Lindsley and associates in the cat. The largest lesions, which most nearly destroyed the extent of the activating system (Figs. 1 *E* and 2, Monkey 9), were not compatible with survival of the animal. It is probable that the sheer bulk of the lesion was responsible for death of the animals, as various surviving preparations were obtained in which injury occurred in essentially every portion of the area involved, with the possible exception of the tectum. Cerebral edema due to brain-stem injury, as described by LeBeau,[6] was not exclusively responsible for death, as it occurred in three of the surviving animals as well as in two of the animals which died.

Somewhat smaller lesions, which were still of sufficient magnitude to destroy a major portion of the activating system, rendered the monkeys totally and permanently helpless and produced a state simulating coma, or at least stupor, in man. As in such states in man, these animals would occasionally respond briefly to intense stimuli by reflex withdrawal of extremities or by diffuse inappropriate movement, at which times the eyes would open in a superficial semblance to wakefulness; but at no time was there any suggestion that the animal was alertly responsive to the stimuli or to his surroundings. The periods of spontaneous activity characterized by running movements in one, and, to a less extent, in another, of these animals occurred most frequently without other evidence of wakefulness. Progressive movements of this type have been described previously by Bailey and Davis[7] and by Schreiner, Lindsley, and Magoun[8] in studies on animals with lesions in this general region, while Sweet, McCulloch, and Snider[9] reported similar repetitive movements on stimulation in the basal ganglia and their interconnections.

While it is possible only to speculate concerning the conscious awareness of these animals from observations on their behavior, somewhat more documentary evidence of their hypersomnolent state is available from a study of serial electroencephalograms made under a variety of circumstances. There was, in fact, considerable discrepancy between the persistently synchronous electroencephalogram of the animals with tegmental lesions and their random behavioral activity when they were stimulated to movement. Aside from movement and "tensing" artifact at these times, there was usually no alteration in the tracing which would suggest desynchro-

6. LeBeau, J.: L'oedème aigu du cerveau par lésions expérimentales du tronc cérébral. Ses rapports avec l'hypertension artérielle. Analogies neuro-chirurgicales, Rev. canad. biol. **7**:254-292, 1948.

7. Bailey, P., and Davis, E. W.: Syndrome of Obstinate Progression in the Cat, Proc. Soc. Exper. Biol. & Med. **51**:307 (Nov.) 1942.

8. Schreiner, L. H.; Lindsley, D. B., and Magoun, H. W.: Role of Brain Stem Facilitatory Systems in Maintenance of Spasticity, J. Neurophysiol. **12**:207-216 (May) 1949.

9. Sweet, W. H.; McCulloch, W. S., and Snider, R. S.: Repetitive Movements on Basal Ganglia Stimulation After Transection of Cerebral Peduncles, Federation Proc. **6**:213 (March) 1947.

nization of the slow-wave activity characteristic of sleep or the unconscious state. Furthermore, stimuli which would arouse the normal animal to wakefulness and desynchronize the electroencephalogram for a long period produced usually no effect on the tracing, or at best, rarely, a slight and incomplete activation for the duration of the stimulus only. It seems justifiable to conclude, therefore, that movements observed in these animals, even when their eyes were open, were random, automatic, or reflex in nature and were not associated with "conscious" awareness.

In two other animals (Monkeys 2 and 4), lesions of comparable magnitude in areas closely approximating those just considered, but sparing the midbrain tegmentum, failed to induce lasting coma or electroencephalographic synchrony. Monkey 2, with a lesion on the medial thalamus, was behaviorly alert, and his electroencephalogram, while initially more synchronous than normal, was readily responsive to arousing stimuli. In the chronic state, his waking and sleeping tracings were indistinguishable from normal. Monkey 4, with a lesion in the bases of the peduncle and pons, was immobilized for the duration of his survival. This akinesis contrasted with the prolonged periods of apparent wakefulness, marked by a relatively desynchronized electroencephalogram. Furthermore, early in his postoperative course the electrocortigram was readily responsive to arousal stimuli. It would appear, therefore, that the akinesis was due to motor paralysis, the cerebral responsiveness to afferent stimulation being left unimpaired.

One of the three surviving animals with significant lesions in the cephalic portion of the brain stem showed some improvement with the passage of time in that periods when the animal was not obviously asleep were somewhat more frequent and the difference between the "waking" and the sleeping tracings was somewhat more apparent (Fig. 9*E*). This improvement was obviously a function of recovering undestroyed brain stem, as the lesion was found to be more posteriorly situated and less complete (Fig. 2, Monkey 8), involving less of the reticular formation, than that in a monkey with a more complete lesion, whose tracing at a comparable time showed no desynchronization whatever, whether during periods of behavioral activity (Fig. 5*F*) or on sensory stimulation (Fig. 5*E*). The third monkey of this group (Monkey 7) showed some evidence of returning behavioral activity until an occlusive vascular accident, destroying more of the remaining activating area, occurred. Subsequently, he was completely akinetic, showing no electroencephalographic or behavioral responsiveness to stimulation. It has previously been suggested that the activating system has a unified function, being responsive as a whole to sensory stimulation of all modalities and exerting a diffuse effect upon the cortex.[2] The evidence from these lesion monkeys would tend to support such a concept, as it appears that the volume of destruction of the area governs the degree of behavioral and electroencephalographic effect on the animal. Indeed, one animal (Monkey 2) had minimal destruction of the activation area (Figs. 1*C* and 2, Monkey 2) and displayed minimal alteration in behavioral and electrocortical activity (Fig. 3). That improvement in responsiveness and in the electroencephalogram of these animals (Monkeys 2 and 8), as well as in Monkey 4, occurred after an initial profoundly depressed state would seem to be of further significance, indicating that the cells in this system may be functionally inactivated, but not necessarily irreversibly destroyed, under certain circumstances, and that their recovery may parallel a returning "consciousness" and improvement in the electroencephalogram. If this

area is of importance in wakefulness or awareness in man, some such mechanism may account for the frequently observed recovery of patients from the prolonged coma of head injury or other origin.

In conclusion, it appears that lesions involving the activating system of monkeys produce even more profound electroencephalographic alteration, hypersomnolence, and behavioral immobilization than do similar lesions in cats. The completeness with which the system is destroyed appears to govern the degree to which such changes will be present in the animal, and it is unlikely that complete destruction is compatible with survival. There is evidence to suggest that subtotal lesions may cause severe changes in the animal initially, due to functional, but reversible, disturbances in the area, and that behavioral and electroencephalographic improvement parallel recovery and return of function of significant portions of the activating system. Presumably, the extent to which recovery will proceed is directly proportional to the area of permanent destruction. Should it ever become feasible to interpret certain physiological and pathological alterations in consciousness clinically in light of these observations in monkeys, it would appear that the central cephalic portion of the brain stem would be a most fruitful area to scrutinize.

SUMMARY

Electrolytic lesions were made in the central cephalic portion of the brain stem of 9 monkeys; as a control, the operation was performed, but no lesion made, in a 10th monkey. These experiments were devised to evaluate the effect on behavior and on the electroencephalogram of destruction of the reticular activating system.

Complete destruction of the area was not compatible with survival of the animals.

Less extensive lesions resulted in a state of behavioral akinesis and hypersomnolence in the monkeys simulating coma in man. The electroencephalograms were characterized by hypersynchrony, which was not responsive to sensory arousal stimuli.

Animals in which lesions of comparable size were made, but which did not involve the reticular activating system, were not similarly affected.

The extent to which the reticular activating system was involved appeared to influence directly the degree to which the behavior and the electroencephalogram of the animals were disturbed.

Miss Wilma Weeks prepared slides of the brains of the animals of this series, and Charles Bridgeman, Timothy Dodge, and Thomas Masterson helped in making the figures.

COMPLICATION OF RABIES VACCINE THERAPY TREATED WITH CORTICOTROPIN

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AND
ALFREDO TOLA, M.D.
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ALTHOUGH the complications of rabies vaccine therapy are rare, the physician always keeps them in mind, owing to their danger.

These complications are of two main types: (1) the local reaction,[1] which is of no importance, and (2) the systemic reaction, which Grinker [2] classifies as myelitic and neuritic. Remlinger [3] describes three clinical types of systemic reaction: (1) acute ascending paralysis of the Landry type, with sudden onset, fever, cephalalgia, restlessness, and paralysis, usually fatal in one-third of the cases; (2) dorsolumbar myelitis, with gradual onset, paralysis, and weakness, and (3) neuritic form, with symptoms of peripheral nerve involvement. The last two types terminate in complete recovery in 100% of cases.

The incidence of systemic reaction is low. Remlinger,[4] in 1905, reported 40 cases of paralysis after 107,712 treatments, and the same author, in 1927, reported 529 cases among 1,164,264 patients treated. Simon [5] gave an average of 0.48 per thousand, with 19 deaths, among 211,774 persons treated, and Mejia [6] reported 24 cases in which paralysis developed after 19,800 treatments.

The main pathological changes which occur in the complications of antirabies treatment have been described by Bassoe and Grinker [4] as constituting a typical toxic reaction in the ganglion cells, vascular endothelium, and oligodendroglia, consisting in perivascular round-cell infiltration with demyelination and axis-cylinder destruction, the *Abbau* of destroyed myelin sheaths in the spinal cords, and the degeneration of the mucin-containing cells.

From the Department of Medicine, British-American Hospital.

1. Geiger, J. C.: Local Reactions of the Pasteur Treatment and Their Time of Appearance, J. A. M. A. **67**:1518 (Nov. 18) 1916.

2. Grinker, R. R., and Levy, N. A.: Neurology, with Chapter on Brain Tumors by Paul C. Bucy, Ed. 3, Springfield, Ill., Charles C Thomas, Publisher, 1943, pp. 755, 213, 788.

3. Neal, J. B., and others: Encephalitis: A Clinical Study, New York, Grune & Stratton, Inc., 1942, pp. 52, 108, 473, 492.

4. Bassoe, P., and Grinker, R. R.: Human Rabies and Rabies Vaccine Encephalomyelitis, Arch. Neurol. & Psychiat. **23**:1138 (June) 1930.

5. Rosenau, M. J.: Preventive Medicine and Hygiene, Ed. 6, New York, D. Appleton-Century Company, Inc., 1935, p. 349.

6. Whitemore, E. R.: Rabies, in Practice of Medicine, edited by F. Tice, Hagerstown, Md., W. F. Prior Company, Inc., 1921, Vol. 3, p. 517.

REPORT OF A CASE

A single white woman aged 40 was admitted to the hospital because of fever, paralysis of the legs with numbness, restlessness, and malaise of 14 days' duration.

The family and past personal histories were noncontributory.

Present Illness.—Six weeks before admission the patient was bitten on the left leg by a rabid dog. Three days later antirabies treatment was started, a total of 17 daily injections being given.

The patient stated that with each treatment she experienced headache a few minutes after the injection. On the 17th day, a few hours after receiving the last injection, she felt very ill; there were cloudiness of vision, flushing of the face, followed by pallor, and a shaking chill. Vaccine therapy was discontinued.

The following day she was examined by a physician, who informed her that everything was normal. She had no symptoms for eight days, when she first noticed that her legs were sore and weak. The following day this weakness and soreness had extended to her hips. She also noted a sensation of cold and a fine tremor of the hands and legs.

Three days later, the 11th day after the last injection of rabies vaccine, she was unable to get out of bed, and her temperature was 37.5 C. (99.5 F.). She consulted a physician, who prescribed penicillin therapy for five days, but without improvement. The pain in the legs became severer and the paralysis more marked. The temperature fluctuated between 37.5 C., in the morning, and 38.9 C. (101.2 F.), at night. She had coarse tremor and soreness of the hands and complained of insomnia and restlessness.

The blood cell count was normal, but, owing to the continuation of symptoms, she was given 12 gm. of terramycin. No improvement was noted, and another physician was consulted, who again ordered a blood cell count. This was found to be within normal limits.

At that time the patient had very severe headaches, paralysis of the legs, insomnia, and marked tremor of the hands, which interfered with grasping. Therapy was again changed to streptomycin and terramycin, but after four days, without any change in the clinical picture, the patient decided to come to the hospital.

Physical Examination.—On admission, the patient seemed apprehensive and restless and appeared ill. The physical examination showed an essentially normal condition except for some rigidity of the neck. The reflexes were hypoactive, particularly on the left side. The abdominal reflexes were absent. Kernig's sign was not elicited, and there were no pathological reflexes. The hands had a marked tremor, and she was unable to stand up because of weakness of both legs, although, with a great deal of effort, she was able to move in bed.

Laboratory Data.—On admission, the blood study showed 12.5 gm. of hemoglobin, 4,300,000 red cells, a hematocrit reading of 42%, and 10,000 white cells. The differential count showed 20 lymphocytes, 1 monocyte, 69 neutrophiles, 9 eosinophiles, and 1 basophile. The Wassermann, Kahn, and Mazzini reactions were negative. The blood urea was 16 mg. per 100 cc. The fasting blood sugar was 100 mg. per 100 cc. The total bilirubin measured 0.50 mg. per 100 cc. of serum. The direct van den Bergh reaction was negative. The sedimentation rate (corrected) was 20 mm. in one hour (Westergren). Urinalysis showed a specific gravity of 1.017; an alkaline reaction; traces of albumin; a negative reaction for glucose, bile, and acetone, and occasional white blood cells in the sediment. Agglutination tests for typhoid, paratyphoid, and brucellosis gave negative results. Culture of blood taken on admission showed no growth after 72 hours. Lumbar puncture showed an initial pressure of 180 mm. of water, clear fluid, 102 cells per cubic millimeter, a 1+ Pandy reaction, 63 mg. of protein per 100 cc., and 38 mg. of glucose per 100 cc. The tryptophan test gave a slightly positive reaction; the differential cell count showed 85 lymphocytes, 4 neutrophiles, and 11 nondifferentiated cells. The culture of the fluid was sterile; the Wassermann reaction was negative, and the colloidal gold curve was normal (0) in all tubes.

Course and Treatment in the Hospital.—Because the patient complained of severe headache, malaise, and fever, she was treated symptomatically with acetylsalicylic acid, phenobarbital, vitamins, and parenteral injections of an antihistaminic. During a period of four days on this treatment the patient showed no improvement, and treatment was then started with corticotropin, 50 mg. every six hours. After 48 hours of treatment, there was marked improvement. The pain

had decreased. She showed only a slight tremor, and her appetite reappeared. On her fourth day of treatment she was able to move without discomfort. The temperature became normal, and the tremor had completely gone. On her 12th day of hospitalization, that is, eight days after corticotropin therapy was begun, her condition was almost normal, and the therapy was discontinued. The following day she was able to get out of bed. A lumbar puncture on the 15th hospital day showed clear fluid with 62 cells per cubic millimeter, a negative Pandy reaction, 31 mg. of protein and 58 mg. of glucose per 100 cc. The tryptophan reaction was negative, and the differential cell count showed 98 lymphocytes and 1 neutrophile. The bacteriological examination showed no pathogens, and the culture was sterile. The patient was discharged on her 18th hospital day, at which time the spinal fluid showed only 10 cells per cubic millimeter, all lymphocytes.

Since discharge, the patient has been observed on several occasions, the last time being two months after discharge, when physical examination showed an entirely normal condition. She is now living an active and normal life.

COMMENT

It has been suggested that the systemic reactions seen with antirabies treatment are due [7] to (1) abortive rabies, (2) infection due to fixed virus, (3) toxins from the rabies virus, (4) toxins from the material used in the manufacture of the vaccine, (5) street virus infection, and (6) anaphylactic reaction.

It has been proved that the complications of antirabies therapy are due to the vaccine, since they may appear in persons who have not been bitten by a dog, but who have received the Pasteur treatment.[3]

Experimental work seems to indicate that the nerve tissue injected is the substance responsible for the reaction, since paralysis may appear after use of nerve tissue from normal animals.[8] This work has not been accepted by Fielder.[7c]

From the foregoing evidence, we seem to explain the paralysis seen after vaccination against rabies by the theory of an anaphylactic reaction, which theory was first advanced by Harvey and McKendrick.[7c] Ratner [9] and Sellers [10] claim that nerve tissue, like any other animal tissue, is a complex protein substance and therefore is capable of stimulating the formation of a specific antibody when injected repeatedly into man. Sellers points out that during the process of immunization against rabies the various forms of allergic response may occur, from circumscribed erythema and delayed urticarial rash to swelling of the joints with fever and malaise. Sellers mentions neuritis and encephalomyelitis with paralysis as other forms of anaphylactic reaction.

On the other hand, the fact that encephalomyelitis occasionally produced after antirabies treatment and encephalomyelitis seen in acute infection present a similar pathological picture does not mean that they are caused by the same agent; as Bassoe and Grinker [4] point out, the pathological response of the nerve tissue is rather stereotyped.

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7. (*a*) Whitemore.[6] (*b*) Babonneix, L., and Sigwald, J.: Flaccid Paraplegia Following Antirabies Treatment, Ann. de méd. **26**:114 (July) 1929; Arch. Neurol. & Psychiat. **23**:1271 (June) 1930. (*c*) Fielder, F. S.: Paralysis During Pasteur Antirabic Treatment, J. A. M. A. **66**:1769 (June 3) 1916.

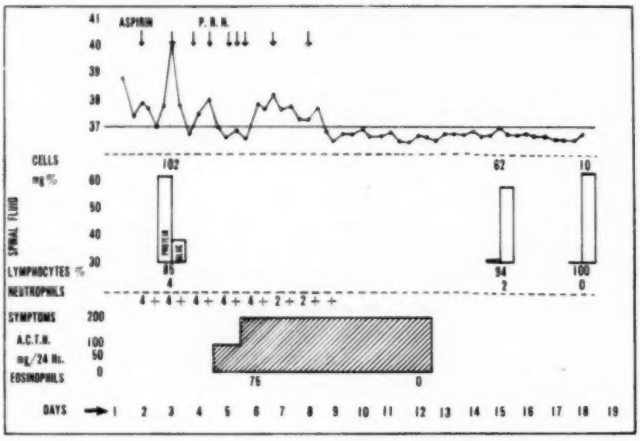
8. Neal and others.[3] Rosenau.[5] Bassoe, P.: Paralysis Following Antirabic Inoculation and Other Forms of Vaccine and Serum Therapy, Arch. Neurol. & Psychiat. **23**:204 (Jan.) 1930.

9. Ratner, B.: Allergy, Anaphylaxis and Immunotherapy, Baltimore, Williams & Wilkins Company, 1943, p. 254.

10. Sellers, T. E.: Rabies, in Harrison, T. R., and Others, Editors: Principles of Internal Medicine, Philadelphia, The Blakiston Company, 1950, Ch. 171, p. 1072.

From this report, it is seen that corticotropin had a definite effect on the clinical and pathological process in a case of paralysis due to Pasteur treatment (Chart). The patient showed great improvement symptomatically. Since we did not have specific treatment, acetylsalicylic acid was given *pro re nata*, and, as one can see from the Chart, the patient began to use less and less acetylsalicylic acid after corticotropin therapy was instituted. The temperature became normal, and spinal fluid values returned to normal.

It has been demonstrated that corticotropin, as well as cortisone, has an antiallergic action, although the exact mechanism is not yet known; it seems to be at the cellular level, giving protection to the cell against the injurious agent.[11] The adrenal steroids do not seem to interfere with the antigen-antibody reaction but interfere with the fixation to the tissues or with the action of histamine.[12]



Clinical data in a case of paralysis due to the Pasteur treatment.

In this case, we had the opportunity to use corticotropin and observe its effects. It seemed to protect the central nervous system of the patient against complications of rabies vaccine, probably by stopping an allergic reaction.

SUMMARY

We present a brief résumé of the reaction seen during rabies vaccine therapy, the incidence of this complication, and the main pathological changes observed. We report a case of paralysis following the Pasteur treatment in which remarkable improvement followed corticotropin therapy.

We enumerate the hypotheses proposed to explain these phenomena and suggest that in the present case it can be proved that the mechanism of the complication involving the central nervous system is an anaphylactic reaction, which can be modified or stopped by the use of adrenal steroids.

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12. Thorn, G. W., and others: Medical Progress: The Clinical Usefulness of ACTH and Cortisone, New England J. Med. **242**:783 (May 18); 824 (May 25); 865 (June 1) 1950.

RESPIRATORY RESPONSES TO STIMULATION OF TEMPORAL POLE, INSULA, AND HIPPOCAMPAL AND LIMBIC GYRI IN MAN

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MANY OBSERVERS have reported changes in respiratory movements induced by stimulation of the cerebral cortex in various animals. The most important of these studies have recently been reviewed by Delgado and Livingston [1] and by Kaada,[2] to which papers the reader is referred. Previous studies on primates which have some bearing on the present study will be summarized briefly.

In the monkey a small area for inhibition of respiratory movements was early found in the lower precentral region (Area 6 B) (Vogt and Vogt [3]; Walker and Green [4]; Smith [5]). A second area which is said to exert an inhibitory influence on respiration in the monkey has been described on the posterior orbital surface of the frontal lobe (Spencer [6]; Bailey and Sweet [7]; Delgado and Livingston [1]; Sachs, Brendler, and Fulton [8]). A third area with similar influence on respiration has been located in the rostral limbic (cingular) gyrus of monkeys (Smith [9]; Ward [10]). Sugar, Chusid, and French [11] noted that respiratory arrest could be obtained also from the anterior portion of the insula of the monkey.

From the Department of Neurology and Neurosurgery, McGill University, and the Montreal Neurological Institute.

1. Delgado, J. M. R., and Livingston, R. B.: Some Respiratory, Vascular and Thermal Responses to Stimulation of Orbital Surface of Frontal Lobe, J. Neurophysiol. **11**:39-55, 1948.

2. Kaada, B. R.: Somato-Motor, Autonomic and Electrocorticographic Responses to Electrical Stimulation of "Rhinencephalic" and Other Structures in Primates, Cat and Dog, Acta physiol. scandinav., Supp. 83, 1951.

3. Vogt, C., and Vogt, O.: Allgemeine Ergebnisse unserer Hirnforschung, J. Psychol. u. Neurol. **25**:277-462, 1919.

4. Walker, A. E., and Green, H. D.: Electrical Excitability of the Motor Face Area: A Comparative Study in Primates, J. Neurophysiol. **1**:152-165, 1938.

5. Smith, W. K.: Representation of Respiratory Movements in the Cerebral Cortex, J. Neurophysiol. **1**:55-68, 1938.

6. Spencer, W. G.: Effect Produced upon Respiration by Faradic Excitation of the Cerebrum in the Monkey, Dog, Cat, and Rabbit, Phil. Tr., London **185B**:609-657, 1894.

7. Bailey, P., and Sweet, W. H.: Effects on Respiration, Blood Pressure and Gastric Motility of Stimulation of the Orbital Surface of the Frontal Lobe, J. Neurophysiol. **3**:276-281, 1940.

8. Sachs, E., Jr.; Brendler, S. J., and Fulton, J. F.: The Orbital Gyri, Brain **72**:227-240, 1949.

9. Smith, W. K.: Functional Significance of the Rostral Cingular Cortex as Revealed by Its Responses to Electrical Excitation, J. Neurophysiol. **8**:241-255, 1945.

10. Ward, A. A., Jr.: The Cingular Gyrus: Area 24, J. Neurophysiol. **11**:13-23, 1948.

11. Sugar, O.; Chusid, J. G., and French, J. D.: A Second Motor Cortex in the Monkey (Macaca Mulatta), J. Neuropath. & Exper. Neurol. **7**:182-189, 1948.

Quite recently Kaada, Pribram, and Epstein [12] observed inhibition of respiratory movements and alterations in blood pressure by stimulation of the temporal pole, including the anterior end of the hippocampal (uncinate) gyrus of the monkey. A more detailed account has been given by Kaada.[2] It was furthermore indicated that all the above-mentioned areas with inhibitory influence on respiratory move-

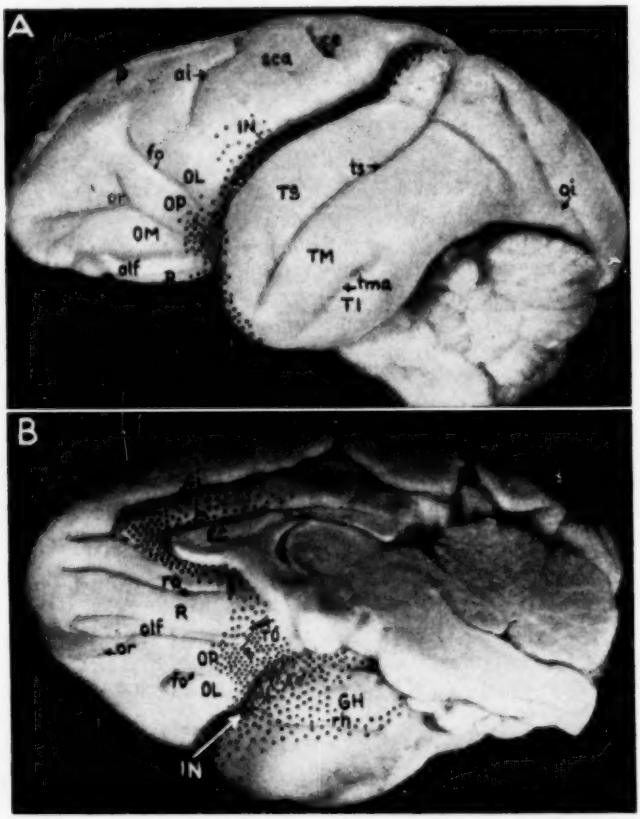

Fig. 1.—Anteroventrolateral (*A*) and ventromedial (*B*) views of the hemispheres of Macaca mulatta. The insula is partly visualized by separation of the temporal and the frontoparietal operculum. The area yielding inhibition of respiratory movements with arrest in expiration is indicated by dots. From Kaada.[2]

ments formed parts of a continuous stretch of responsive cortex extending from the temporal pole through the anterior portion of the insula, the posterior orbital surface, and the subcallosal region to the rostral limbic area (Fig. 1). Within this stretch of basally and mesially situated cortex two optimal zones were located, one in the

12. Kaada, B. R.; Pribram, K. H., and Epstein, J. A.: Respiratory and Vascular Responses in Monkeys from Temporal Pole, Insula, Orbital Surface and Cingulate Gyrus: A Preliminary Report, J. Neurophysiol. **12**:347-356, 1949.

region of the postorbital surface, insula, and temporal pole, and another around the genu of the corpus callosum. The responsive areas appear to be covered by a phylogenetically ancient type of cortex, either by allocortex or by isocortex showing characteristics of transitional cortex.

In man inhibition of respiratory movements has been observed by stimulation of the lower precentral region (Bucy and Case [13]) and the posterior orbital surface of the frontal lobe (Livingston, Chapman, Livingston, and Kraintz [14]). Recently Pool and Ransohoff [15] have recorded respiratory responses, both arrest and acceleration, from the anterior limbic region in man.

The present study deals with the effect on respiratory movements of stimulation of the temporal lobe, the insula, and the hippocampal and limbic gyri in the conscious patient. In addition, information has been obtained concerning the patients' subjective experiences during stimulation of points with inhibitory influence on respiratory movements. The patients were operated upon in 1949 by Dr. Wilder Penfield for the relief of cerebral seizures. Some of the results have been presented as a preliminary report (Penfield [16]; Kaada [2]). During the preparation of this paper similar observations were reported by Liberson, Scoville, and Dunsmore.[17]

METHOD

The exposed cortex was stimulated, with the use of local anesthesia only, by means of a Rahm stimulator (sine waves) with intensities varying from 1 to 4 volts and with frequencies of 30 to 60 cps. The procedure for stimulation used at the Montreal Neurological Institute has been described elsewhere (Penfield and Erickson [18]). Respiratory movements were recorded by means of a closed air system. This consisted of a corrugated gum rubber tube fastened by a leather strap around the chest of the patient and connected with a thick tubing to a Marey tambour provided with an ink-writing lever. The respirogram was recorded simultaneously with, and on the same paper as, the electrocorticogram. In four patients alterations in respiration were studied by direct observation of the movements of the chest.

RESULTS

A summary chart of points which by stimulation produced cessation of respiratory movements is given in Figure 2. Observations could be made only from a very limited number of points for each of the eight patients studied, and no complete map of the regions yielding respiratory responses in man can at present be offered. The results demonstrate, however, that arrest of breathing can be obtained in the conscious patient by stimulation of points in the same general region as that outlined above for the monkey.

13. Bucy, P. C., and Case, T. J.: Cortical Innervation of Respiratory Movements: I. Slowing of Respiratory Movements by Cerebral Stimulation, J. Nerv. & Ment. Dis. **84**:156-168, 1936.

14. Livingston, R. B.; Chapman, W. P.; Livingston, K. E., and Kraintz, L.: Stimulation of Orbital Surface of Man Prior to Frontal Lobotomy, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:421-432, 1948.

15. Pool, J. L., and Ransohoff, J.: Autonomic Effects on Stimulating Rostral Portion of Cingulate Gyri in Man, J. Neurophysiol. **12**:385-392, 1949.

16. Penfield, W.: In Symposium on Clinical and Electrical Aspects of Temporal Lobe Disorder, held by American Electroencephalographic Society, Atlantic City, N. J., June, 1950.

17. Liberson, W. T.; Scoville, W. B., and Dunsmore, R. H.: Stimulation Studies of the Prefrontal Lobe and Uncus in Man, Electroencephalog. & Clin. Neurophysiol. **3**:1-8, 1951.

18. Penfield, W., and Erickson, T. C.: Epilepsy and Cerebral Localization: A Study of the Mechanism, Treatment and Prevention of Epileptic Seizures, Springfield, Ill., Charles C Thomas, Publisher, 1941.

In the temporal region points yielding respiratory inhibition were found on the anterior portion of the hippocampal gyrus and on the temporal pole proper. The latter points were located on its ventral surface, just lateral to the rhinal fissure (Fig. 2*B*) and on the medial aspect of the pole, close to the insula (Fig. 2*A*), whereas the lateral surface, which was stimulated repeatedly, was found unresponsive except for its very tip. Complete arrest of breathing also followed stimulation

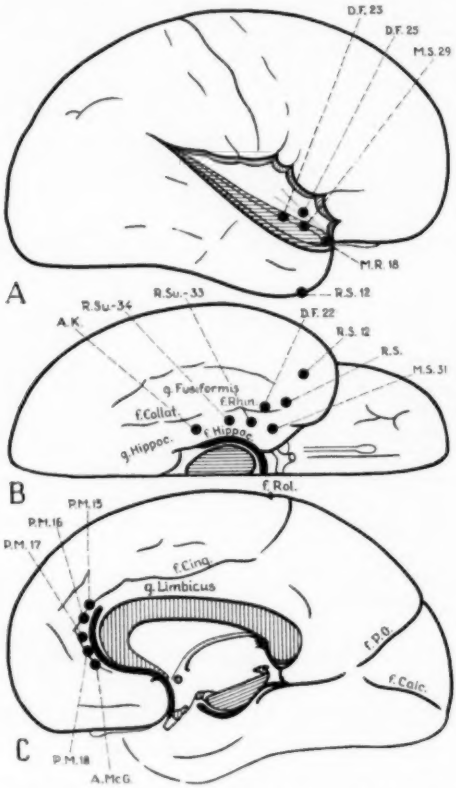

Fig. 2.—(*A*) lateral, (*B*) ventral, and (*C*) medial views of the right hemisphere of man. In the lateral view the insula has been visualized by retraction of the frontoparietal operculum and by horizontal section of the first temporal convolution. Solid circles indicate points which on electrical stimulation produced cessation of respiratory movements in expiration. All points (from eight patients) were transferred to the right hemisphere. Local anesthesia only was used.

of the anterior portion of the insula, which in two patients had been exposed after removal of the anterior portion of the temporal lobe (Fig. 4).

On the medial surface of the cerebral hemisphere respiratory inhibition was obtained from points in a rather narrow zone in the precallosal region of the limbic gyrus (Fig. 2*C*). Stimulation of points situated 0.5 to 1 cm. in front of this zone

was without any effect. In the present study no opportunity was offered to explore the supracallosal and subcallosal limbic regions or the orbital surface of the frontal lobe.

The respiratory arrest obtained from the above-mentioned areas invariably occurred with the chest assuming an expiratory position (Fig. 3 *A*). The effect appeared promptly upon application of the stimulus and lasted during the entire period of stimulation (varying from 6 to 30 seconds), being occasionally interrupted by a deep breath. It is of interest to note that mechanical stimulation of the areas concerned also was observed to produce cessation of breathing. Thus, in two patients suction in and about the anterior portion of the hippocampal gyrus resulted in complete respiratory arrest (Fig. 3 *B*), in one instance for as long as 56 seconds. Suction outside these areas was not observed to give any significant changes in respiratory movements.

An interesting feature was the observation that the patients were able partly to overcome the respiratory arrest when asked to count during the stimulation. But

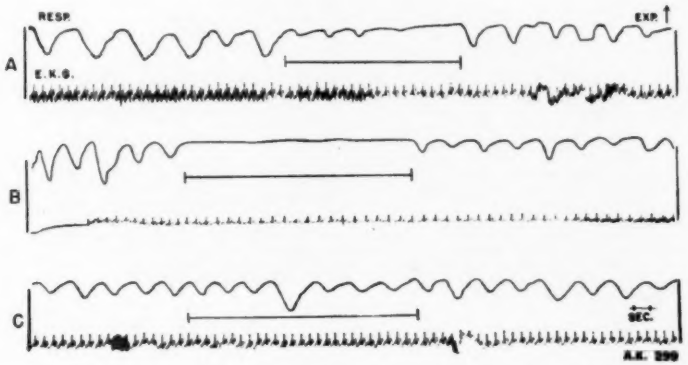

Fig. 3.—Upper tracing, respirogram; lower tracing, electrocardiogram.

A, arrest of respiratory movements resulting from electrical stimulation (60 cps, 4 volts, 12 seconds) of Point *AK* (Fig. 2 *B*) on the hippocampal gyrus. A decrease in pulse rate from 62 to 58 beats per minute was followed by an increase to 72 per minute a few seconds after the end of stimulation.

B, mechanical stimulation (suction) in and about the anterior portion of the hippocampal gyrus producing the same effect as did electrical stimulation. The heart rate decreased from 72 to 56 beats per minute.

C, control stimulation (60 cps, 4 volts, 16 seconds) of the lateral surface of the temporal lobe; no respiratory response.

difficulties were encountered in talking, obviously owing to the interference with the respiratory apparatus, as demonstrated in the cases cited. It is, furthermore, of considerable interest to note that the respiratory arrest in some instances was associated with impaired consciousness, with a tendency to close the eyes, and with a feeling of tiredness and sleepiness, but apparently without complete loss of responsiveness unless an epileptic seizure was produced. Brief abstracts of the protocols of six patients follow.

In P. M., aged 24, repeated stimulation (30 cps, 3 volts) of the left anterior limbic region around the genu of the corpus callosum (Fig. 2 *C*, Points *P. M. 15, 16, 17, 18*) resulted in

immediate respiratory arrest. The patient was asked to count, and stimulation of the same points produced slowing of the counting (repeated five times). For instance, stimulation at count "4" resulted in slowing at count "5" and in complete apnea from count "8" on, followed by deep breaths at count "11."

In A. McG., aged 21, stimulation (60 cps, 5 volts) of a point just in front of the genu of the corpus callosum on the right hemisphere (Fig. *2C*, Point *A. McG.*) produced complete cessation of respiratory movements. This stimulation was repeated when the patient was not aware of its application. Respiration stopped as long as the stimulus was applied, about 30 seconds, the period of apnea being interrupted only by a deep inspiration. When the patient was asked why he stopped breathing, he said he did not know he had done so. He was told to look into the eyes of the observer; but during stimulation fixation was lost, and the eyes were slowly wandering about in all directions.

In D. F., aged 26, stimulation (30 cps, 4 volts, 12 seconds) of a point on the ventral surface of the temporal pole, close to the rhinal fissure (Fig. *2B*, Point *D. F. 22*) caused the patient to say, "A little hard to get my breath," or "Funny feeling like before an attack." (Her aura was a fear-like, substernal sensation.) Stimulation repeated without warning produced an immediate

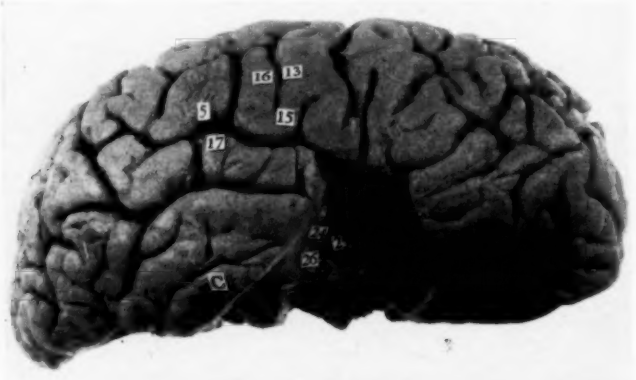

Fig. 4 (D. F.).—Removal of the anterior half of the right temporal lobe, including the anterior end of the hippocampal gyrus and the amygdaloid nuclear complex. The operative removal was reproduced on a cadaver brain with the aid of drawings and photographs taken during the actual operation. The numbers represent the points stimulated. Stimulation of Point *25* on the insula caused respiratory arrest and the epileptic seizure recorded in Figure 5. Arrest of respiration was also obtained from Point *23*, on the medial surface of the temporal lobe, in juxtaposition to the insula, and from Point *26*, in the white matter of the temporal lobe.

inhibition of respiration. The patient was observed to make attempts to speak, but had obvious difficulties and could not vocalize. She observed about 20 seconds after the beginning of the stimulation: "I think this is just a slight one [attack]."

Point *D. F. 23* (Fig. *2A*), on the medial surface of the first temporal convolution in juxtaposition to the anterior insula, was stimulated. The patient was asked to count. Stimulation (30 cps, 4 volts) resulted in inhibition of respiratory movements, and counting was slowed. After withdrawal of the stimulus, the patient seemed a little confused and said, "Oh, I went to sleep."

In R. Su., aged 20, stimulation of the anterior end of the hippocampal gyrus and the adjacent portions of the temporal pole (Fig. *2B*, Points *R. Su. 33, 34*) reproduced the patient's aura of abdominal sensation and feeling of familiarity. These feelings were associated with respiratory arrest, drowsiness, and difficulty in keeping the eyes open during the stimulation.

In two patients stimulation of points yielding arrest of breathing resulted in an epileptic seizure, beginning with immediate cessation of respiratory movements,

indicating that respiratory arrest can be the initial phenomenon in epileptic seizures originating from these regions of the cerebral cortex.

D. F., aged 26, experienced an aura of fear-like, substernal sensation. At times the aura was followed by automatism, with loss of consciousness, chewing movements, turning of the head and eyes to the left and then to the right, and pulling of the mouth to the left. Occasionally there were generalized convulsive movements.

At the operation a definite abnormality was found in the anterior part of the first temporal convolution on the right side, extending mesial to the insula and to the ventral surface of the temporal lobe, including the uncus. Electrical stimulation of points on the temporal pole (Fig. 2 *A* and *B*, Points *D. F. 22, 23*) and the anterior portion of the insula (Fig. 2 *A*, Point *D. F. 25*) produced arrest of respiratory movements.

One of the stimuli (60 cps, 4 volts, 6 seconds) applied to the anterior portion of the insula (see also Fig. 4, *25*) produced an electrocorticographic seizure discharge lasting 40 seconds

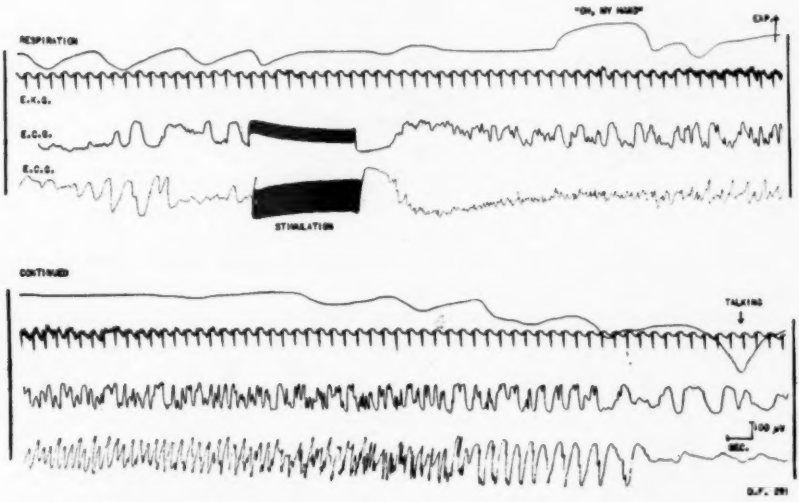

Fig. 5 (D. F.).—Epileptic seizure produced by electrical stimulation (30 cps, 4 volts, 4 seconds) of Point *25* (Fig. 4) on the anterior portion of the right insula. First line, respiratory movements; second line, electrocardiogram; third and fourth lines, electrocorticograms (one pair of electrodes on the right insula, the other on the lateral surface of the right temporal lobe), continuous record. The electrical seizure discharge lasted 40 seconds and was accompanied by a clinical seizure, starting with immediate arrest of respiration in expiration. See text.

(Fig. 5). The respirogram demonstrated a prompt arrest of respiratory movements, with the chest assuming an expiratory position. The pupils dilated. After 12 seconds the patient said, "Oh, my hand," thus breaking through the respiratory arrest. In about half a minute the respiratory movements reestablished themselves, despite continuation of the seizure. The clinical attack outlasted the electrocorticographic seizure discharge by about three minutes, during which period the patient was unresponsive and exhibited automatic behavior and chewing movements.

M. R., aged 29, since the age of 7 years has had frequent seizures consisting of sensation in the head, followed by some change in hearing and vision. Things seem to appear farther away, or she may observe that she sees things with an increased degree of clearness. This aura may be followed by loss of consciousness, during which have been noted marked salivation, swallowing, mastication, audible borborygmus, pupillary dilatation, flushing of the face, and confused automatic behavior.

Electrical stimulation (60 cps, 3 volts, 11 seconds), without warning, of the first temporal convolution, close to the temporal pole (Fig. 2*A*, Point *M. R. 18*), precipitated a clinical epileptic seizure similar to the patient's habitual attacks: Immediately after the application of the stimulus the patient said, "Oh, now I'm having an attack," or "Oh, I'm really having an attack." She immediately stopped breathing, and the thorax assumed an expiratory position. Apparently, she tried to answer the question of the observer, but had obvious difficulty and only hummed a little. She became drowsy and looked tired, closed her eyes partially, but not more

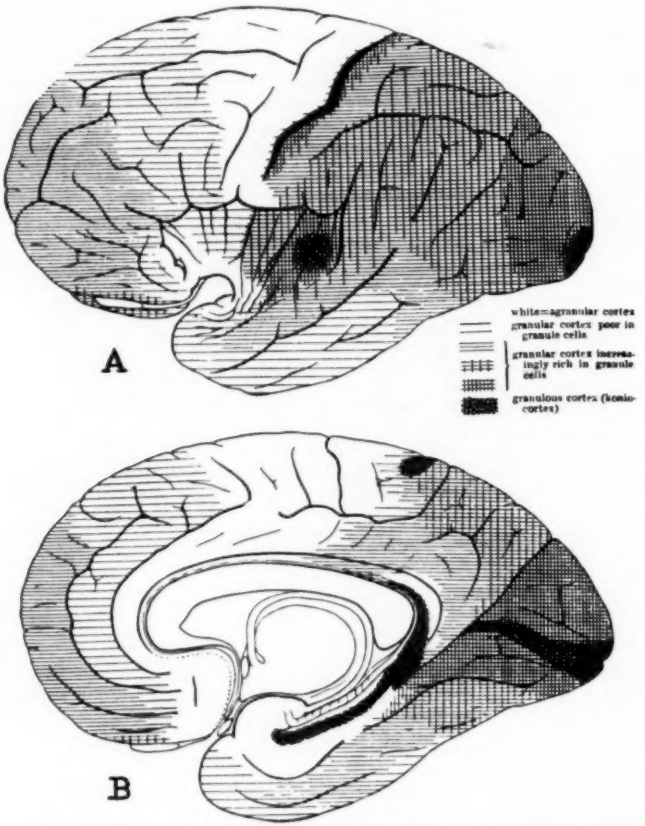

Fig. 6.—Distribution of agranular (white) and different types of granular and granulous cortex in man, according to von Economo (The Cytoarchitectonics of the Human Cerebral Cortex, translated by S. Parker, London, Oxford University Press, 1929).

so than that it could be seen that both pupils were dilated. In the middle of the attack, which lasted 37 seconds, regular swallowing movements were observed. The lower part of the left cheek bulged a little, owing to an increased amount of saliva, and gurgling sounds, which accompanied the swallowing and the tongue movements, could be heard. There was no mastication. At the end of the seizure, she took a deep breath, and she was again able to answer questions.

COMMENT

The present study demonstrates that stimulation of parts of the insula, temporal pole, and anterior hippocampal and limbic cortex in the conscious man produces respiratory arrest of the same character (in expiration) as that observed in the anesthetized monkey. A comparison of the responsive points in man (Fig. 2) with the responsive region as previously determined for the monkey (Fig. 1) shows a great deal of coincidence. In man the area includes, besides the anterior ends of the limbic and hippocampal gyri and the anterior portion of the insula, the adjacent cortex of the ventral aspect of the temporal pole lateral to the rhinal fissure, and the cortex of the medial surface of the pole close to the insula. The lateral aspect of the temporal pole has so far, in man, not given any significant responses. It is possible that with the great development of the temporal lobe in man the responsive cortex has been displaced more ventromedially than in the monkey.

A comparison of the extent of the agranular and sparsely granular cortex of the regions in question (Fig. 6) with the responsive points (Fig. 2) suggests that these points in man, as in the monkey, fall within this agranular and sparsely granular division of the limbic and hippocampal gyri, the insula, and the adjacent temporal pole.

It appears likely that the areas are not specifically respiratory in function, but have their effect on respiration as part of a complex pattern related to other functions. Their relation to the central vagal representation, as well as to the sense of smell, has been considered in detail elsewhere (Kaada [2]).

The feeling of tiredness and sleepiness, associated with a tendency to close the eyes and impaired consciousness, which in some patients accompanied the cessation of breathing, is of considerable interest. As shown in the monkey, the respiratory inhibition obtained by stimulation of the anterior limbic gyrus seems to be part of a more generalized inhibitory influence on somatomotor activities (Smith [9]; Ward [10]; Kaada [2]). Spontaneous movements and the knee jerks may be inhibited as well. The same has been demonstrated for the postorbital surface, insula, and temporal pole in monkeys and cats (Kaada [2]). Electrical stimulation of the latter regions, as well as of the anterior limbic cortex, was found to produce (*a*) an almost immediate and complete cessation of spontaneous movements, such as struggling and shivering; (*b*) an immediate inhibition of motor after-discharges (when not too violent) resulting from stimulation of any point in the sensorimotor cortex, and (*c*) reduction or abolition of cortically induced movements and spinal reflexes. These inhibitory effects in monkeys were frequently associated with a sleep-like response with closure of the eyes and diminished resistance to passive motion and palpation of the muscle bellies, a response which was first described by Smith [9] in stimulation of the anterior limbic area. Whether the cortical zones under discussion in some way are involved in the sleep mechanism can at present be only a matter of speculation. There can be little doubt that areas giving respiratory arrest may also produce changes in consciousness, as also indicated by the studies of Liberson and associates.[17]

From the standpoint of epilepsy, it is of interest to note that in two patients respiratory arrest was recorded as the initial phenomenon of the onset of seizures induced by stimulation of points yielding cessation of breathing. In major epileptic seizures, with tonic and clonic convulsions, there is naturally arrest of respiration

(in inspiration), due to spasmodic fixation of the chest. Hughlings Jackson,[19] however, drew attention to the fact that in some slight epileptic attacks belonging to his "uncinate group of epileptic fits" asphyxia can occur without spasm, or real convulsions. An illustrative case (F. F.) was reported in which attacks started with a "funny feeling" and smacking of the lips. Then "the patient (his lips) 'turned blue'; his eyes were half closed. His arms dropped *soft*,[20] not *stiff*.[20] When he came around, he *drew a long breath* [20] and began to breathe easily, and then seemed 'dazed and muddled' and asked 'unlikely questions.' After the attack he complained of a nasty taste."

The most frequently occurring phenomena in the uncinate group were a dreamy state, a crude sensation of smell and taste, chewing and tasting movements, epigastric aura, and a sense of suffocation. Hughlings Jackson considered the blue, purple, livid, or dark-pale color of the face frequently seen in slight attacks of this group as signs of asphyxia. Since, in monkeys, alterations in blood pressure may result also from electrical stimulation of the areas in question (Kaada and associates [12]; Kaada[2]; Wall and Davis [21]), it appears likely that the changes in the color of the face may be due partly to a direct cardiovascular influence from the discharging lesion, and that they are not secondary to the arrest of breathing only.

Hughlings Jackson suggested that the interference with respiration in some patients of the uncinate group was due to inhibition of the medullary respiratory center by discharge spreading from the uncinate region to "the cortical centre for arrest of respiration," which a few years previously was thought to have been located on the posterior orbital surface of the frontal lobe (Spencer [6]). However, as demonstrated in the monkey (Kaada and associates [12]; Kaada [2]), the arrest of breathing obtained by stimulation of the hippocampal gyrus and the adjacent region of the temporal pole is not due to indirect activation of the inhibitory cortex of the posterior orbital surface, since complete section of the uncinate fasciculus or complete cortical isolation by deep incisions of the separate areas failed to alter the respiratory responses from the hippocampal gyrus and temporal-pole region. This indicates that the inhibitory effects from the latter regions as well are mediated directly to subcortical structures.

We agree with, and should like further to emphasize, the suggestion made by Hughlings Jackson [19] of ". . . particular inquiry and careful observation regarding degrees of asphyxia in slight paroxysms of the group of cases of epilepsy [being dealt] with; the colour of the face (especially of the lips), the state of the chest walls and abdomen, and the attitude of these parts, inspiratory or expiratory."

Finally, it is of interest to note the relations of the temporal and insular respiratory areas to epileptic automatism. In reviewing the localization points of epileptic automatism produced by stimulation of the cortex on the operating table at the Montreal Neurological Institute, one is struck by the fact that the points overlap

19. Jackson, J. H.: On Asphyxia in Slight Epileptic Paroxysms: On the Symptomatology of Slight Epileptic Fits Supposed to Depend on Discharge-Lesions of the Uncinate Gyrus, Lancet **1**:79-80 (Jan. 14) 1899. Jackson, J. H.: Selected Writings, edited by James Taylor and others, London, Hodder & Stoughton, Ltd., 1931, Vol. 1, p. 462.

20. Italics are Hughlings Jackson's.

21. Wall, P. D., and Davis, G. D.: Three Cerebral Cortical Systems Affecting Autonomic Function, J. Neurophysiol. **14**:507-517, 1951.

those for respiratory arrest in these areas, though respiratory arrest did not always accompany automatism (Feindel, Jasper and Penfield, paper in preparation). Seizures resembling epileptic automatism and starting with respiratory inhibition have also been induced in cats by stimulation of the anterior end of the hippocampal gyrus (Kaada [22]).

The stimulus inducing the respiratory arrest may also produce depression of the electrical activity of the brain. In other cases, however, no change in the electrocorticogram occurs, or after-discharges of various types may be recorded during and after the period of apnea (Fig. 5). Thus, the lack of relationship between depression of electrical activity and arrest of respiration should be clearly emphasized.

SUMMARY

Results of electrical stimulation of the temporal lobe, the hippocampal and limbic gyri, and the insula in man, with recording of respiratory responses, are reported.

From points indicated in Figure 2 inhibition of respiratory movements in expiration was obtained. The responsive points were located in the anterior end of the hippocampal gyrus, the ventral and medial surfaces of the temporal pole, the anterior portion of the insula, and the anterior limbic gyrus. The posterior orbital surface and the subcallosal region of the frontal lobe were not stimulated.

Arrest of breathing was recorded as the initial phenomenon in epileptic seizures induced from these areas (Fig. 5).

Associated with the respiratory inhibition there was frequently impaired consciousness, a feeling of tiredness and sleepiness, and a tendency to close the eyes.

Dr. Wilder Penfield carried out the operative procedures and electrical stimulations upon which this report is based, and assisted in preparing the manuscript.

22. Kaada,[2] pp. 225 and 242.

EMOTIONAL ISSUES RELATED TO CERTAIN CASES OF BLEPHAROSPASM AND FACIAL TICS

ORTHELLO R. LANGWORTHY, M.D.
BALTIMORE

THE ETIOLOGY of many neurologic symptoms is still obscure and effective treatment elusive. New and larger frameworks for consideration of these problems are needed. I have attempted in small groups of patients to investigate emotional factors, either as accentuating or being related in some causal way to certain neurologic illnesses, such as narcolepsy and multiple sclerosis. This application of psychiatric thinking in the field of neurology meets considerable prejudice. It should be possible to use this method with an open mind, gradually collecting data in an attempt to learn whether this approach is valid or useful. No general conclusions can be derived from a small series of patients.

Blepharospasm and facial tics are flamboyant, attention-attracting abnormalities, which cannot easily be concealed. In an attempt to use psychotherapy in a small number of patients with such disorders, it appeared that certain of the patients were concerned with similar problems in interpersonal relationships. Further, an understanding of their underlying attitudes may be useful in the strategy and tactics of treatment. In this group the distressing facial disfigurements may be considered as unconscious warnings displayed by the patients as indications of their own unreliability and their hostile attitudes. The issues seem to revolve around the matter of giving and receiving, with emphasis placed on getting the best of the bargain by methods not completely honest. Like the heroine of Hawthorne's story who wore the letter *A* for adultery, they display a symbol for others to see. It can also be postulated that patients who have blepharospasm and cannot open their eyes are not able to look at the facts. From a diagnostic viewpoint, these patients may be thought of as suffering from a conversion hysteria, although the issues involved possibly divide them into a separate group.

The four patients were seen for a number of interviews. These visits were designed largely so that I might get better acquainted with their problems, and the present paper is concerned with the patients' attitudes and the issues which might be related to their symptoms. However, the matter of treatment was always involved. I was careful to make clear to these persons that it might not be possible to offer them relief.

Although hypnosis may improve or alleviate the symptoms for a time, I have had no prolonged success with this method. The purpose of corrective therapy is to deal with the problem in the solution of an emotionally charged issue between the patient and the therapist. For purposes of convenience, treatment may be divided into three phases, or periods. The first period consists of getting acquainted. The patient

From the Henry Phipps Psychiatric Clinic, The Johns Hopkins University.

develops a relationship with the physician, and the therapist gains a grasp of the issues involved. The second period is a time when the patient's attitudes are actually challenged by the therapist around a specific emotionally laden issue involving the patient's problem. The third period is a time when the patient struggles to find some new method of making a satisfactory relationship with the therapist after the old methods have been rendered unsatisfactory.

REPORT OF CASES

These introductory statements may be illustrated by case material. The first case was carried to a successful conclusion.

CASE 1.—*Introductory Period.*—Mrs. A., a married housewife aged 48, came for treatment during World War II. I saw her once a week for about a year. She was an enormous woman whose eyes were closed tightly by spasm of the surrounding muscles. In order to see, she had to force and hold one eye open with her fingers. Under these conditions the other eye would sometimes open voluntarily. She was a person of limited intellectual ability. This had an influence on the subject matter of our visits. She explained that three years earlier she began to blink her eyes, and soon they closed. There was less spasm of the eyes in the morning, and occasionally they would open spontaneously. She was greatly handicapped in her housework, to the point that she peeled potatoes with her eyes closed. She seldom went out of the house because she was distressed to have other people see her difficulty. When asked whether she was nervous, she said, "I never had any worries, but I am sensitive. If people say nasty things to me, it eats and eats. I have a younger sister whose husband left her when her child was 5 months old, and I raised the child. Then my sister became interested in a bad man. She talked mean to me because my mother would not let him in the home. I speak to her, but she does not bother to answer me."

On her first visit she expressed fairly benign attitudes toward most members of her family. Her mother, a widow of 77, ran a small grocery store. "She has a wonderful disposition, and everyone likes her." An older sister came to be known as the good sister, and the younger sister, as the bad sister. The older sister was a widow, who lived with the mother and helped with the store. "She is nervous. She takes all the responsibility, and no one helps her." This sister brought the patient to see me each week. Indeed, the day of her visit was of the nature of an outing or a holiday for Mrs. A. Her sister took her shopping, and they usually had a drink and luncheon at a good restaurant before keeping my appointment. The patient enjoyed wearing different dresses and hats for me to admire. She was especially interested in good food, and this was the subject of much of our conversation. Her husband collected waste kitchen grease during this war period. She tended to apologize for him and his dirty work. She kept pointing out that she was a clean woman and kept a clean house. She said she felt it was a mistake that she did not have children, but added, "If they treated me like my sister treated my mother, I would not want children. My sister called my mother a hypocrite."

During the early visits the patient became fond of me and seemed to open her eyes more freely. "If you will speak kindly to my eyes, they will open. They are stubborn." She also felt free in discussing her attitudes toward her family more honestly. She explained that she had spent her life in doing things for the family, but none of them appreciated her kindness. She did more for her mother than anyone, but the mother liked even the bad younger sister better. She talked each week with anger and spite about new and petty quarrels with the family or neighbors. There was a good deal of variation in her mood, and at the time of her periods she was depressed and her eyes were closed tighter. She talked about obsessive trends in seeing that the lights were turned out and the doors locked. Excessive hand washing was often a problem.

Period of Challenge.—The period of getting acquainted lasted about five months, until the situation became intolerable, owing to emotional problems pointed up between patient and therapist. The patient would overwhelm me with gifts of food which she brought each week. In days when food was severely rationed, she would bring half a ham or a pound of butter. She explained that her husband in his occupation was in a position to receive extra food coupons.

At the same time, she suggested that her eye trouble was caused or made worse by the war situation, which deprived her of many pleasures. Riding in public conveyances was upsetting to her, and she would be more comfortable in a car. She felt that frequent automobile trips to the country would improve her condition. She asked me several times to write the ration board and request that she be given an extra gas allotment. I told her that I could not accept any more gifts, and she left in an angry mood.

On the following week we had our most productive interview. The patient was hurt, hostile, and aggressive and used several methods in an endeavor to control the situation. She began by saying that she had a dreadful dream on the night after our previous interview and she had been depressed and had slept poorly since. In the dream she walked to her mother's home, to see a crepe on the door, and learned that her mother was dead. She cried when she told me that she felt her mother did not really love her, even though she gave her mother so much. She told me for the first time of the circumstances leading up to her eyes closing. She had quarreled with her younger sister and insisted that the sister return a diamond pin which a former employer gave the patient and the patient had loaned to the sister. The patient wanted to get it back from the bad sister to give to the good sister. During the quarrel her sister said "You are an evil woman." That day her eyes began to close. She said that she was disappointed and hurt that I would not accept presents. She tried to place the blame for my refusal on my wife. "She ought to know I do not think of you in that way." She explained that if you do good things for others, good will come back to you. She said she felt that people could never like her unless she gave them something. For the first time she attacked my smoking by saying that she never allowed smoking in her house because it was a dirty habit. She was resentful that I would not help her obtain more gasoline coupons. When she left my office, she had trouble in finding the money to pay me.

Period of Resolution.—During the next five or six months she remained critical of me and tried in every way to get me to adopt a different attitude toward her. She was doubtful of my ability to help her and said that I resembled an ophthalmologist whom she had seen previously. She said this man talked mean to her and made her eyes worse. She constantly talked of quarrels with her family, which all followed a rather simple and stereotyped pattern. They all had to do with the fact that others did not appreciate her efforts to do things for them. During this time she seemed reassured by the fact that I held my position but tried to be friendly and helpful.

An emotional crisis with her husband seemed to be a great factor in her final improvement. She had always claimed a good relationship with him, and indeed he seemed to go far out of his way to make her life comfortable and happy. As time went on, this tolerant attitude of his seemed to become more and more intolerable to her. She told me that she flirted with waiters in restaurants, and she often said that she would like to make her husband jealous. For months she seemed to go out of her way to precipitate a quarrel with him. This quarrel finally developed in the following way. As Easter approached, the patient bought herself a complete new wardrobe, but her husband bought only a new hat. While house cleaning before Easter, she burned its box and her hubsand's new hat before he had worn it. She said she was working with her eyes closed and she thought the box empty. For the first time the husband blew up and showed his anger and resentment. He was able to tell her off and then resume his tolerant attitude. This seemed to stabilize the patient greatly, and her eyes began to improve. She seemed to feel that both her husband and her physician understood her hostile attitude, but liked her in spite of it. Although she found that she could keep her eyes open all day without trouble, she had to find some acceptable and mechanical resolution. She went to an optometrist, who built spurs on the frames of her glasses to "hold her eyes open." She was free from her symptoms and stopped treatment.

In summary, this patient had great difficulty in looking at an honest evaluation of herself. When her family reacted to her aggression and said unkind things to her, she felt abandoned. When the therapist and then her husband were able to face her hostility and yet stand behind her with friendly support, she was able to abandon her symptoms.

CASE 2.—The second patient was carried only into the second stage of therapy because he had to leave the city. The problem was clearly defined, but the clinical result was only partly satisfactory.

Mr. B., a 58-year-old sugar planter from a country of Spanish culture, complained, "When I speak I close my eyes." Indeed, on speaking, all the facial muscles took part in ugly grimaces. The muscles would often go into such spasm that he would sit back quiet and exhausted. He was a politician and liked to make speeches but was handicapped by the facial tics. He wished to associate with important people but felt uncomfortable and self-conscious because of the spasms. The tic developed a year before I saw him, at the wedding of his oldest daughter. He had opposed the marriage on the grounds that the man whom she was to marry came from an inferior social background. He said that he cried at the wedding and that his eyes began to close then. Gradually any attempt to speak made the eyes close. Previously he had violently opposed the marriage of his two sons because he felt they also married beneath their social position. He considered his wife soft and sentimental because she stood by the children in their marriage plans.

During the early course of our interviews he spent most of the time in boasting of his social and financial status. He was making his third trip around the world with his wife and three younger daughters. His father had been a senator and an influential man. He himself was a great friend of the president of his country. He talked in great detail of the many jewels he gave his wife and their cost. On a previous voyage he had lost $5,000 in gambling. He would stay only at the best and most expensive hotels and went to the greatest effort to obtain a highly desirable room.

Gradually he suggested that he did not always act in an entirely ethical manner. He told of a bribe of $35,000 which he gave to obtain an important office. He was double-crossed and did not gain this position. He kept a mistress and often went out with women, explaining that he showed his wife the greatest consideration. He also stated that people always took advantage of him in spite of his kindness and generosity. He thought that everyone cheated him and that he never obtained full value for his money. While under treatment with me, he took dancing lessons but said they would teach him no new steps unless he paid them more and more money. His views as to his own personal values changed at different interviews. Once he listed the highest values in order as "money, position, and career." At another time he said, "I do not know why my sons do not have confidence in me. I fight for a higher position. I look for personal values. Money is easy to get."

The patient talked a great deal of his father and tended to imply that his father was a fine man and he himself was a failure. He described his father as strict. When he was a young man, the patient revolted against his father's influence and seldom thereafter listened to his father's advice. "My father was very brave. I do not have a third of his bravery. He was never defeated in any way." The patient talked often of his own fears. At times he indicated that he was a failure because he did not have his father's high standards. He thought of both his mother and his wife as weak and sentimental. While he showed some admiration for his sons, he did not approve of their plans and felt hurt that they did not confide in him.

The patient had great difficulty in sleeping. He was tense, worried about his health, and considered his hypertension as a great threat to his life. He was constantly fearful that something would happen to him or to his daughters. He was meticulous about his appearance and constantly worked to impress other people with his importance.

The second phase of treatment began just before he had to leave the city to continue his trip. It was precipitated by giving him a bill. He became angry and distressed, saying that he was being exploited again. He said he was especially hurt that a physician in whom he had confidence should treat him in this way. Although he had spoken on each visit of his great wealth, he thought that my bill was far too large, and he suggested a much smaller figure. Three further interviews were devoted to discussion of this financial matter. During these periods he seemed in many ways more honest and sincere. The facial tics were less prominent, and indeed they stopped completely at times. He seemed more comfortable in this controversy than he had in the previous interviews. However, he had to leave before there was time to discuss or resolve larger problems. Subsequently, he has visited the city two or three times. He called on me in the lobby of the hospital but did not come to my office for treatment in order that he might avoid the problem of paying me.

In summary, this man considered his father a man of great integrity and attainment. The patient was unwilling to accept his father's ideals because he thought of his father as too strict and dictatorial. He himself tried to obtain success similar to his father's by less honest means and laid great stress on money and social position. When his children and his wife rejected his ideals and way of life, his facial tics developed. Treatment finally challenged his shady methods of living and his feeling that he was always cheated and double-crossed by others. Further interviews would have given an opportunity for dealing with these troublesome attitudes.

CASE 3.—The third patient had chorea, rheumatic fever, and cardiac damage in childhood. The choreic movements of the face cleared, but facial tics appeared again at the time he became engaged. This patient's treatment has not yet been followed to a successful conclusion, owing to the appearance of other symptoms which demanded immediate attention.

Mr. C., a 47-year-old public servant, sought help for the facial tics because he feared they would hinder further advancement in his career. He had a constant feeling that he must stretch his face. The movements were manifested as winking of the left eye, wiggling his nose, or pulling his mouth to one side. At the time of his marriage the movements were more violent and there were grunting sounds, which disturbed his wife. "I used to make noises like a bunch of pigs."

Mr. C. had two severe attacks of chorea. A history of the second attack, which occurred at the age of 12, is recorded in the records of this hospital. Abnormal winking movements were seen in the right eye. He completely lost control of the right arm and leg. The movements were first observed at boarding school, where it was thought he was trying to avoid work. The hospital record also gives a diagnosis of mitral stenosis and mitral and aortic insufficiency. He was advised to avoid violent exercise. In spite of the cardiac damage, the patient lived an unusually active life. He became an excellent tennis player, served several years in the Army, and later was active physically. He was never challenged on physical examination because of heart trouble. In the weeks before coming to see me, he was conscious of unusual fluttering feelings over his heart, which he compared to the movements of a wounded bird.

The patient was a large, manly man; he was friendly with the therapist but spoke of all his family in a loud voice filled with irritation and exasperation. He described his mother as a "cruel and inhuman woman with no love and no mercy." He was an only child, and his mother wanted a girl instead of a boy. She kept him in curls and dresses until he was 4 years old. As a child he was sickly and a "sissy." His mother often beat him with a lash. The parents separated when he was 12, and his father died soon thereafter. The patient disliked his stepfather and later sued his stepfather for a debt which the latter refused to pay. His mother kept him in boarding school until he ran away to the Army, at the age of 18.

Before his marriage, his wife made fun of him because he was under his mother's thumb, and his mother placed great restrictions on his staying out in the evening. He was married at the age of 19, without his mother's knowledge, and he and his wife kept the arrival of a baby a secret until after it was born. Some time during the engagment the facial tics began. He complained that no one gave them anything when they were married. The marriage was described as a continual battle. His wife was cold sexually. The patient was known to have had several extramarital affairs. He and his wife never could agree about the raising of their only child. His wife later obtained a job which annoyed the patient. She drank heavily, bringing bottles home and hiding them around the house. The patient described his mother-in-law as a snooping, nagging woman, who had interfered in the marriage. His wife made fun of the facial tics. "My wife starts arguments at the table. I am even-tempered and try not to be exasperated." Arguments often led to broken furniture and physical violence.

Attitudes about money were discussed frequently. At the first interview Mr. C. explained that he was always a little in debt but that his creditors were willing to wait because he always paid his bills eventually. He said that he had a friend who wanted to pay for his psychiatric treatment. It developed that he and his wife did not agree about the way in which money was to be spent. The patient had several expensive hobbies which he wished to support. He justified these hobbies on the basis that they made friends for him and tended to advance his career.

His wife wished more money for clothes and for the home. They both enjoyed taking long trips in their car and borrowed money to finance these excursions. Consequently, the patient had to pay a little money here and a little there, so that he would not be hurried to meet his obligations. Later, he said that his wife always wanted more than her share of everything, while he felt they should divide equally. As an illustration, he said that his wife would eat all four pieces of chicken left in the icebox rather than leave two for him. His greatest objection to his wife's drinking was that she did not save any for him.

Mr. C. showed many perfectionistic and obsessive trends. He was extremely particular about keeping records and stayed up late at night putting his work in order. In the course of 10 visits, he showed increasing anger and irritability. He said no kind things about his family, except that he showed some tolerance for his son. I sent him bills, which he did not mention or acknowledge in any way. He seemed more and more tense. The second stage of treatment seemed to be near and the challenge appeared to relate to the matter of taking care of his bill. At this point, the patient called to say that he was having difficulties with his heart, and later his wife told me that he had entered a hospital. His wife suggested that physicians were uncertain whether his complaints were of organic or functional origin. Anxiety symptoms may possibly account for his cardiac complaints.

In summary, this patient had chorea as a child, with facial tics as part of the choreic picture. He showed cardiac damage but led an unusually active life. As a child, he was caught in an entangling relationship with his mother. Since he thought that she caused him to be a sissy, he made himself into a manly man. Facial tics returned with great severity when he married secretly a woman who made fun of his close relationship with his mother. Apparently, his fear of his mother made him keep the marriage a secret. He was always hostile and critical of people close to him, feeling that they always took advantage of him. He felt that no one gave him his share. He found it difficult to face the matter of paying bills. There were obsessive and perfectionistic trends. The interviews seemed to release further anxiety, expressed as cardiac symptoms. It seems clear that the patient was unable to be honest in close relationships, but always found some justification for his behavior. We may speculate about the meaning of the facial tics. He described noises which he made as similar to pig's grunting. Some of his behavior and worry over getting his share, or more than his share, suggested that he was a pig. The wink might be interpreted as a sexual advance toward women. He had been involved in extramarital affairs, which caused a good deal of trouble with his wife.

CASE 4.—The final case concerns a 69-year-old woman who traveled across the country each year for a diagnostic study because she was concerned about her health. I saw her for four interviews in three years because of facial tics. These tics began three years before our first interview. She had noticed that there were three or four types of facial movement, involving particularly the left side of her face. About the cause of the tic she said, "I am satisfied it is not my eye, but it may be my brain." She feared senile changes in her brain. The movements were made worse by public speaking and excitement. She was interested in speaking at meetings of the societies to which she belonged.

The patient presented herself as a business woman who had many irritations and aggravations because other people were dishonest and tended to cheat her. In telling her story, she explained that she had finished normal school and taught grade school in the South for 12 years. She then became dissatisfied with her work and returned to New York to live with her parents. She felt that she should care for them because she was the only surviving child. At the age of 36, she married a man who was 12 years older. There were no children, and her husband soon became an invalid from diabetes. Her parents died and left her a good deal of property in the West. She enlisted a woman friend to go with her to help manage her business. She said, "I had a lot of property dumped on me, and there were complications. I was very upset. I was having a number of operations, and my woman friend wanted to help. Every mean trick

was done to me. At one time I had five lawsuits at once. It shattered my confidence in human nature." She returned to visit her husband periodically until he died, and then moved West to live alone in a big house. Periodically she visited her woman friend.

She talked at length about her mother, whom she described as a Southern aristocrat who never did any work and never took care of the children. The patient had four siblings, who all died at an early age. The next younger brother was the mother's favorite because he was sickly, and the patient was jealous of him. She implied that her siblings died because of her mother's neglect. "My mother did not know what was going on. She wanted to paint and write poetry."

When I first saw Mrs. D., she was sitting in the lobby of the hospital with papers spread out around her, writing vigorously. She explained that she belonged to six patriotic organizations and held office in several of them. She was always writing and working in their behalf. She was also interested in genealogy and in travel. She frequently mentioned that she was lonely and had no one to take an interest in her. She had been devoted to her woman friend for many years but realized that this woman was too old and sick to offer her much support.

About half of each visit was devoted to discussing her distress that everyone tried to take advantage of her in financial matters. She was especially suspicious of men and felt that they were careless in business. A boy whom she had hired to help her tore up a telegram which would have been useful in winning a lawsuit. Her husband destroyed valuable papers which she had placed in the safety deposit box. She had so many vexations over the payment of her income taxes that she placed all her assets in government securities to avoid further aggravation.

The facial tic had begun suddenly three years earlier, when she was spending Christmas with her woman friend. When I tried to learn more of the circumstances, she became disturbed and hostile. She did say that she was more devoted to her woman friend than she ever had been to her husband. This had led to marital discord. She told me that her husband was able to support her adequately and there was no financial reason for her to leave him. She felt guilty that she had deserted him when he was sick. She said defensively that he understood that she must collect money from her father's estate. Since she complained that she was lonely, I suggested that she help finance young people in their education and, in turn, enlist some friendly interest from them. She rejected any such idea with the statement that she was completely occupied with her patriotic societies. Just before our last interview she told me that she had just placed her woman friend in a home for the aged. My patient said that she herself enjoyed her independence and would keep her own home as long as possible.

Treatment in this case was on a supportive basis. The patient seemed to gain some comfort from yearly diagnostic studies. She enjoyed repeated visits with several physicians. She never allowed herself to be entangled in a more complex treatment situation.

In summary, this patient was an autistic woman with some tendency to paranoid projection. She formed few close relationships. She was concerned about money and always felt that people were taking advantage of her. This led to quarrels and lawsuits. The tic developed when she was 66 years old. Her only close friend was becoming senile and could no longer offer emotional support. The patient worked hard in organizations and obtained her satisfaction from them. The choice of patriotic societies suggests a close identification to the mother, who considered herself a Southern aristocrat. The tic was accentuated by her speaking in public and thus disturbed her greatest source of satisfaction. The patient showed some guilt that she could give only to organizations, and not to people close to her.

COMMENT

The recovery of the first patient from blepharospasm and facial tics was a surprising and thought-provoking experience for the physician. When this woman first appeared for treatment, considerable strength was required to force and hold an eye open. For a long time the situation was discouraging. Early in the treatment hypnosis and suggestion gave some relief, which was not sustained. After a

number of interviews the fundamental issues which caused difficulties in interpersonal relationships were clarified in the mind of the therapist. The patient tried to bribe him to support her shady dealings. The refusal to accept presents disturbed the patient greatly and led immediately to further revelations. The patient's feelings took a more realistic channel, so that she was able to express hostile feelings and work actively to manipulate the situation. Her more realistic attitude grew slowly as the therapist held his ground in a tolerant and supportive way. The patient-therapist relationship was a copy of her previous relationships, with the difference that the physician did not call her an evil woman but endeavored to help her.

This experience led the therapist to speculate as to whether other patients with blepharospasm and facial tics had similar interpersonal problems and whether a knowledge of these problems would aid the therapist in guiding the treatment situation. When the second patient came for treatment, it was evident that he would remain in the city for only a limited period. He complicated the situation by stating that he would stay until his dental work was completed. He thus manipulated treatment for the facial tics into a secondary position. On some days all his worries were focused on his hypertension. He did not inquire into the cost of psychiatric therapy but presented himself as a person of enormous financial resources. The therapist was equally at fault in that he did not bring this matter up for discussion or ask for payment at frequent intervals. It was evident from the first that this patient could not deal in a forthright or honest way with interpersonal relationships. As the interviews continued, it was also clear that the patient felt rejection from his family because of his attitudes and had some conscious awareness of the underlying problem. Again, the therapist could not visualize the issue which would develop between himself and the patient until it appeared. Since the patient was prepared to leave the city, treatment could not be carried to a conclusion.

By the time the third patient presented himself, the therapist was sensitive to the issue and the way it could be used in treatment relationship. From the first interview, discussions were guided to the fundamental problem. The patient described himself as a good man who never received his share. He made it clear that those close to him were rejecting in their attitudes toward him. He talked quite frankly about his difficulty in handling money and paying bills. It appeared that the issue would develop around the matter of paying for his treatment. At the time of his first visit the patient presented two defenses to prevent clarification of this issue. He said that people were willing to wait for a long time for him to pay them because they knew he always paid his bills. He told the therapist that a friend of his would pay for his psychiatric treatment. The therapist hesitated to deal with these two evasions at the first interview. Later the patient made no response to financial statements. Gradually he became more distressed and anxious. Cardiac symptoms led to his entering another hospital. The fourth patient was concerned with problems similar to those of the other three. She did not remain in the city for prolonged treatment. She paid her bills through the hospital, so that no personal issue about money developed.

Although the facial tics may be thought of as conversation symptoms, these four patients were particularly concerned with problems of a type usually related to obsessive behavior, and they all showed perfectionistic trends. The first was interested in problems of cleanliness and checking and rechecking. The second was ambitious as to social and political position. The third was successful in his work

and in his hobbies. The last patient was a leader in the organizations in which she worked. Each was concerned with the problem of giving and receiving; each had a feeling of not receiving a fair share. The first patient felt that she must always give in order for people to like her, and even then she did not receive much appreciation. The second stated that he was always cheated. The third thought that he did not receive his share. The fourth actively participated in litigation, protecting herself from men who threatened to cheat her. In each case there were long discussions of money.

The blepharospasm and facial tics appear to develop relatively suddenly. After one has become well acquainted with the patient, it is sometimes possible to understand the circumstances which precipitated the abnormal movements. These circumstances have to do with rejection by some person important to the patient. The first patient closed her eyes when her sister called her an evil woman. She tried to present herself as a person who gave her life to doing kindly things, whereas actually she constantly said spiteful things about others. Her sister's attack and rejection produced an extremely traumatic blow. The second patient stressed the importance of money and social position. When he objected to his daughter's choice of a husband, the whole family rejected his attitudes. The facial tics developed at his daughter's wedding. The third patient never explained the onset of the facial tics as clearly. The woman who was to be his wife taunted him about his submissive and dependent relationship to his mother, and the subsequent marriage was a rebellious gesture of independence of his mother. The tics developed when he became engaged and were so severe that he grunted like a pig. It seems likely that he was rejected by his mother. The fourth patient acquired a tic at the age of 66, when she was spending Christmas with a woman friend with whom she had been closely associated for many years. Probably she had a better relationship with this woman than with any other person. If this woman had criticized the patient's poor relation to her husband, it might have constituted a severe rejection.

The facial tics manifested themselves in ways which served as severe handicaps in interpersonal relationships. Two of the patients used public speaking as a technique of communication. The tics were greatly accentuated by public speaking. The woman whose eyes closed became largely dependent on other people. The tic irritated the wife of the other patient and threatened to interfere with advancement in his work.

SUMMARY

Four patients with blepharospasm or facial tic were seen for a number of interviews in an effort to understand their attitudes and the life issues with which they were struggling. All four were rather perfectionistic persons who were concerned with the problem of giving and receiving. Each had a feeling of not receiving a fair share. They appeared to try to get the best of the bargain by methods not completely honest. The blepharospasm or facial tic appeared to develop rather suddenly, in relation to rejection of his attitude by some person important to the patient. During the course of the interviews these problems of giving and receiving became an active issue between the patient and the therapist. In the setting of a good working relationship the patient's attitudes could be challenged by the therapist. In one of the cases treatment was continued until the issue was resolved and the patient was relieved of symptoms. This series is too small to be significant, but is presented in the hope that it will stimulate further observations.

STUDIES ON BLOOD-BRAIN BARRIER WITH RADIOACTIVE PHOSPHORUS

II. Hypophysis and Hypothalamus in Man

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GENERAL principles regarding the blood-brain barrier of the animal brain measured with P^{32} have been reported in an earlier paper.[1] It was found that P^{32} can be used, more accurately than any other agent, to determine the permeability of the barrier under physiologic conditions. In these earlier experiments, after intravenous injection of the tracer, there was found in the pituitary gland of the rabbit a higher P^{32} content than in the central nervous system. This phenomenon was explained by the fact that the hypophysis lacks any particular barrier and incorporates phosphates as other organs do, an explanation supported by vital-dye studies.[2] No definite difference in behavior could be demonstrated, however, between the hypothalamus and the rest of the brain, nor could a distinction be made in the various lobes of the pituitary gland itself. It did not appear possible to carry out such determinations on the brains of small animals within tolerable limits of error. Furthermore, a considerable variation in the anatomy of these structures is to be found in different species. For these reasons human brains and pituitary glands were used in the present studies.

MATERIAL AND METHODS

Postmortem material from 12 adults, ranging in age from 32 to 74 years, was used. None of the patients had degenerative, predominantly vascular, or infectious disease of the central nervous system. In 10 of the patients P^{32} was routinely administered to localize a brain tumor. Recent craniotomy had been carried out on nine of them. Two patients had malignant tumors outside the nervous system and had not undergone any recent operation. All but three patients had been given a standard single intravenous dose of 2 mc. of radioactive phosphate. In all, a satisfactory electrolyte and water balance had been maintained, and none had prolonged circulatory failure. On five patients frequent daily blood determinations of the P^{32} level were made. Death occurred 6 hours, 16 hours, and 2½, 3, 3½, 4, 6, 7½, 8, 10, 11, and 20 days after the injection of the tracer. In most cases autopsy was performed one to five hours after death. Various parts of the brain, the entire hypothalamus, and the pituitary gland, as well as parts of the liver and abdominal muscle were removed in all cases, and blood was collected from the heart. In three cases tissues from almost all the organs were analyzed.

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2. Broman, T.: The Permeability of the Cerebrospinal Vessels in Normal and Pathological Conditions, Copenhagen, Ejnar Munksgaard, 1949, pp. 1-92.

All specimens were stored without chemical fixation at a temperature of —20 C. The steps taken to determine the radioactivity varied slightly from case to case. As a routine, radioautographs of slides of sagittal or transverse sections of the pituitary gland and hypothalamus, 0.5 to 2 mm. thick, were made on Kodak® No-Screen X-Ray Film, according to the method of Steinberg and Selverstone.[3] The activity was high enough to allow short exposure times (24 to 96 hours) without significant loss of activity for future procedures. After the autographs had been developed, the sections were photographed or accurately drawn and then dissected according to anatomic landmarks and density differences of the autographs. The pieces were placed on aluminum planchets, weighed, dried, and counted for radioactivity by scalers. In some cases the hypothalamus was divided into as many as 15 to 20 pieces. Analysis of the P^{32} content was made in six to eight areas of the pituitary gland. Alternate or symmetrical parts were prepared histologically to serve as microscopic controls. To establish a firm base line, various parts of the cortex and of the white matter of the brain and cerebellum were analyzed for P^{32} content. The final data were computed in counts per minute per milligram of fresh tissue. Corrections were made for quantitative purposes to compute all data to 2 mc. of P^{32} given per 70 kg. of body weight.

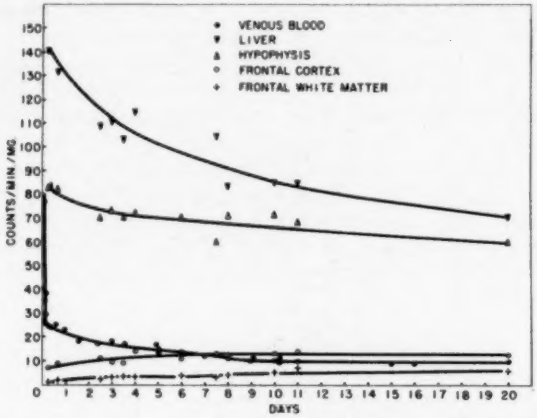

Fig. 1.—P^{32} concentration of various organs following intravenous injection of 2 mc. of the tracer per 70 kg. of body weight.

Radioautography of microscopic sections was also done in several cases. For this purpose, transverse sections in three standard planes of the hypothalamus were used: The hypothalamus was cut (1) across the level of the infundibulum, or slightly behind it; (2) through the tuber cinereum, halfway between the infundibulum and the anterior edge of the mamillary bodies, and (3) through the corpora mamillaria. Microscopic sections of 20-μ thickness were prepared from these cut surfaces of the unfixed material by cutting it with the microtome at a temperature of —10 C. in the modified cryostat of Linderstrøm and Lange. The average time of exposure on Eastman "No-Screen" X-Ray Film was four weeks. Every third section was stained and used as a histologic control.

The total phosphate of the tissues was determined by the method of Fiske and Subbarow.

RESULTS

Our data indicate that the uptake of P^{32} by the brain from the blood is a slow process indeed. Figure 1 shows these data for human organs calculated to a standard

3. Steinberg, D., and Selverstone, B.: Radioautography of Cerebral Tumors Employing P^{32}, Proc. Soc. Exper. Biol. & Med. **74**:304-308, 1950.

dose of the tracer and to the same body weight. There was an abrupt fall in the P^{32} concentration of the blood within four hours after the injection, but afterward there was only a gradual, slow decline in activity. One has to bear in mind, however, that the whole blood was used for these determinations and that a large percentage of the radioactive phosphate was organically bound after the first few hours in the red blood corpuscles.

The liver incorporates the tracer rapidly and in large amounts but, owing to the easy permeability of its cells, loses an appreciable part of its P^{32} with time. Abdominal muscle, on the other hand, better conserves its phosphorus acquired during the phase of high plasma concentration, presumably because of the low permeability of the muscle cells. The pituitary behaves rather like the liver, with a rapid initial incorporation of P^{32}, the concentration decreasing to a less extent than in the liver. In contrast to these tissues, the brain incorporates P^{32} from the blood at a slow rate; it reaches its maximum uptake only 7 to 10 days after the injection and keeps its P^{32} concentration at practically the same level for weeks, despite the steady loss of the tracer in the whole organism by excretion. Both the diffusion of P^{32} from plasma to the cells of the central nervous system and the uptake of inorganic P^{32} into organic combination are slow (Samuels, Boyarsky, Gerard, Libet, and Brust [4]). Other tissues with slow metabolism, such as bone, also take up P^{32} slowly. The basic difference between them and the brain is that brain can take up P^{32} rapidly under special circumstances; the rate of its transphosphorylation is, as a matter of fact, even faster than that of the liver once the blood-brain barrier is bypassed (Bakay and Lindberg [5]).

If the pituitary-white matter ratio or the liver-white matter ratio is plotted against time (Fig. 2), a characteristic declining curve becomes apparent. The pituitary-white matter ratio reaches its maximum very shortly after intravenous injection of P^{32} and then declines gradually from 70:1 to 20:1 and, finally, to 10:1, where it remains for a prolonged period. There is no difference between man and other mammals; similar ratios were found for rabbits (80:1 in 24 hours) and rats (90:1 in one hour, 82:1 in two hours). The counts per milligram of wet tissue were used in presenting these data; to give them in terms of specific activity (number of counts per milligram of phosphorus of the tissue) would not have changed them significantly, as the total phosphorus content of these tissues is similar and varies from 250 to 380 mg. per 100 gm. of tissue (brain, 250 to 280 mg.; liver, 300 mg.; pituitary, 320 to 380 mg.). The gray matter of the brain, whether cortical or nuclear, concentrates about two to five times as much P^{32} as the white matter, although the total phosphorus content of the former is only 10% higher than that of the latter. This constant increase in the specific activity of the cortex was already observed and described by Roeder [6] It may correspond to the total capillary length of the tissue, which is about three to four times as great in the cortex as in

4. Samuels, A. J.; Boyarsky, L. L.; Gerard, R. W.; Libet, B., and Brust, M.: Distribution, Exchange and Migration of Phosphate Compounds in the Nervous System, Am. J. Physiol. **164**:1-15 (Jan.) 1951.

5. Bakay, L., and Lindberg, O.: Studies on the Role of the Cerebrospinal Fluid in Brain Metabolism as Measured with Radioactive Phosphate, Acta physiol. Scandinav. **17**:179-190, 1949.

6. Roeder, F.: P^{32} im Nervensystem: Der Phosphataustausch des Nervensystems untersucht mit Hilfe der Isotopenmethode, Göttingen, Musterschmidt, 1948, pp. 1-32.

the white matter. The radioactivity of the cerebellum was less than that of the cerebral cortex, but more than that of the white matter.

Examination of the pattern of distribution of P^{32} in various parts of the pituitary gland reveals first the approximate equality in the number of counts in the anterior

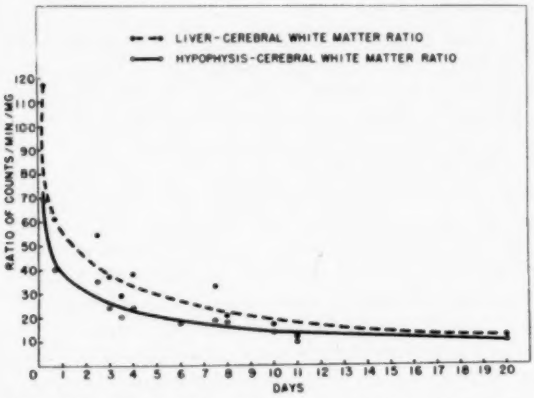

Fig. 2.—Pituitary-white matter ratio (solid line) and liver-white matter ratio (line of dashes) plotted against time.

*P^{32} Content of Various Parts of the Central Nervous System**

Patient	Sex	Age, Yr.	Time Elapsed After Intravenous Injection of 2 Mc. of P^{32} per 70 Kg. of Body Weight	Frontal Lobe		Cerebellum	Hypophyseal Lobe		
				Cortex	White Matter		Intermediate		
							Anterior	Part	Posterior
P. F.	M	68	6 hr.	7.0	1.2	3.0	78.0	50.0	90.0
G. LeB.	F	34	16 hr.	9.0	2.0	3.5	79.0	....	87.0
A. G.	M	44	2½ days	11.0	2.0	4.0	71.0	....	68.0
A. S.	F	65	3 days	9.5	3.0	6.0	71.0	41.0	80.0
J. M.	M	63	3½ days	9.0	3.5	...	62.0	57.0	85.0
M. C.	F	32	4 days	14.0	3.0	9.0	72.0	....	74.0
W. M.	M	44	6 days	11.0	4.0	9.0	68.0	57.0	72.0
E. M.	F	38	7½ days	13.0	3.2	7.0	61.0	....	56.0
L. B.	M	60	8 days	12.5	4.0	6.0	78.0	....	55.0
C. R.	M	52	10 days	13.0	5.0	7.0	66.0	50.0	84.0
M. LeC.	M	74	11 days	14.0	7.0	9.0	74.0	55.0	66.0
Ch. F.	M	41	20 days	12.5	6.0	10.0	56.0	43.0	66.0

* Values are expressed in counts per minute per milligram of tissue.

and in the posterior lobe (Table; Fig. 3). In most cases the difference between these two parts was not significant, whether examined a few hours or a few weeks after the injection of the isotope. The P^{32} concentrations of the anterior and posterior lobes were equal in 3 of 12 cases; in 3 others the anterior lobe was more active, and in 6 cases the posterior lobe was more active. In nine cases, however, the difference was less than 15%, and in only three cases was the difference between 20

and 30%. One of the patients (M. C.) was pregnant, and the anterior lobe of her pituitary gland showed pronounced hyperplasia; yet there was no change either in the amount of the tracer deposited or in its distribution. Some evidence indicated, however, that there might be a difference in the degree or rate of uptake of P^{32} among various types of hypophyseal cells. Floderus' study [7] of the microscopic morphology of the pituitary gland showed that in some cases a dense conglomeration of eosinophile cells can be seen on median sections of the posterolateral parts of the anterior lobe, the chromophobe and basophile cells concentrating in the anterior parts and in the midline. Such a grouping of cells was observed histologically in P. F. (Fig. 4 *A*), who died six hours after the administration of P^{32}. The corresponding radioautogram (Fig. 4 *B*) revealed diminished P^{32} concentration in the area occupied by acidophile elements as compared with the rest of the anterior lobe.

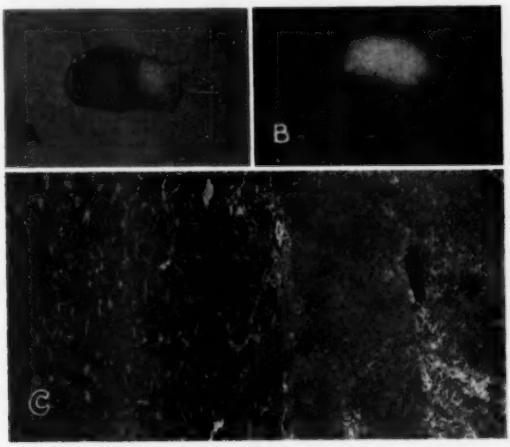

Fig. 3.—*A*, sagittal section of hypophysis of W. M. obtained six days after injection of 2 mc. of P^{32}.

B, radioautograph of same specimen as that shown in *A*; thickness, 1 mm.; exposure time, 52 hours. There is no difference in density between the anterior and the posterior lobe.

C, microscopic section indicating absence of intermediate lobe.

The extreme anatomic variability of the intermediate lobe of the human hypophysis is well known. Sometimes it is well developed and visible with the naked eye, and microscopic study reveals colloid-filled follicles. In most cases, however, it consists chiefly of a small band of connective tissue separating the main lobes. There were examples of both these variations in our material. In seven cases the intermediate lobe was present to such an extent as to lend itself to isolated P^{32} determinations, and it was found to contain only 70% of the average amount of the tracer per milligram found in the whole hypophysis. The range of variation was from 55 to 80%. Consequently, the intermediate lobe concentrates less phosphate than the pars anterior and the pars nervosa and the same amount as the infundibulum.

7. Floderus, S.: Untersuchungen über den Bau der menschlichen Hypophyse mit besonderer Berücksichtigung der quantitativen mikromorphologischen Verhältnisse, Acta path. et microbiol. Scandinav., Supp. 53, pp. 1-276, 1944.

The P^{32} deposit of the infundibulum was equal to that of the intermediate lobe of the hypophysis, and less than that in the anterior or posterior lobe. In some cases the counts were the same in various portions of the pituitary stalk; in others they diminished slightly in the upper end. The P^{32} concentration in the adjacent, medial part of the tuber cinereum (eminentia saccularis) was slightly less than the concentration encountered in lower parts of the stalk; but it was still higher than that in other areas of the brain. Comparative data in our cases reveal another interesting fact. Figure 1 shows that the P^{32} content of the hypophysis decreases with the lapse

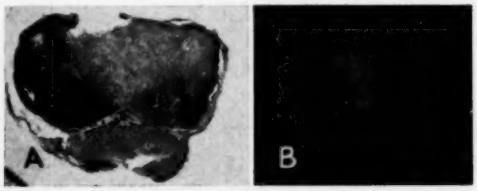

Fig. 4.—Median horizontal section of hypophysis of P. F., who died six hours after administration of 0.9 mc. of P^{32}.

A, microscopic picture, phosphotungstic acid-hematoxylin stain. Dark areas in posterolateral parts of anterior lobe (*x*) reveal a conglomeration of acidophile cells.

B, radioautograph; exposure time, 47 hours. Density in the areas occupied by acidophile cells is decreased.

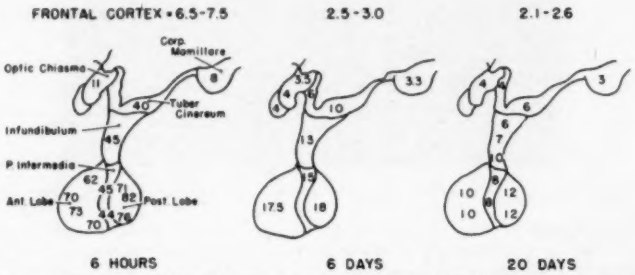

Fig. 5.—P^{32} concentration in various parts of hypophysis, infundibulum, and tuber cinereum, 6 hours, 6 days, and 20 days following intravenous injection of 2 mc. of the tracer. Data are calculated on the arbitrary basis that the activity of the central white matter is 1 count per minute per milligram of tissue.

of time, as does that of other parenchymatous organs of the body. The central nervous system, on the other hand, accumulates radioactive phosphate slowly but steadily with time. Interestingly, not only the infundibulum but also the tuber cinereum behaves like the pituitary gland, and not like the brain itself. They concentrate P^{32} heavily in the first few hours after administration of the tracer, then lose it gradually. If the data are calculated on the basis of the arbitrary assumption that the white matter of the frontal lobe contains 1 count per milligram of tissue in one minute, and if all the other data are computed according to this standard (Fig. 5), it is evident that the pituitary stalk, although concentrating 45 times as much P^{32} as the white matter in 6 hours, contains only 13 times as much in 6 days and 6 to 10 times

as much in 20 days. The ratio of the radioactivity of the medial part of the tuber cinereum to that of the frontal white matter was 45:1 in 6 hours, 10:1 in 6 days, and 6:1 in 20 days. This decrease in ratio is identical with the decrease in the ratio of the radioactivity of the hypophysis to that of the white matter.

The lateral and posterior parts of the tuber cinereum contain less P^{32}, although significantly more, still, than the cortical or nuclear gray matter of other areas of the brain. The radioactivity of the tuber cinereum also diminishes gradually in the cranial direction (Fig. 6). The ventromedial nucleus of the hypothalamus concentrates about 30% less P^{32} than the eminentia saccularis, and the dorsomedial nucleus contains even less. Above and beyond this area, the concentration of radioactive

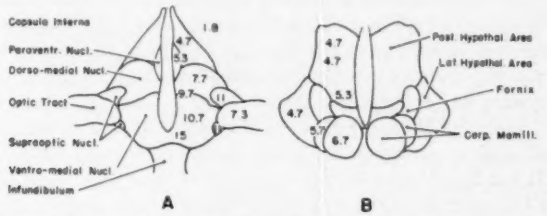

Fig. 6.—P^{32} concentration in hypothalamus, 7½ days after intravenous administration of 2 mc., shown in transverse sections through the tuber cinereum, behind the level of the infundibulum (*A*), and through the corpora mamillaria (*B*). On the arbitrary assumption that the activity of the central white matter is 1.0 count per minute per milligram of tissue, that of the frontal cortex is 4.1 to 5.0 counts per minute per milligram of tissue.

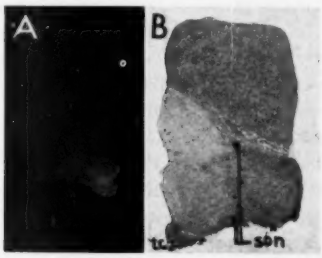

Fig. 7.—*A*, radioautograph (enlarged) of microscopic section (30 μ) of hypothalamus. The specimen was obtained 7½ days after administration of 2 mc. of P^{32}. Exposure time, four weeks.

B, section corresponding to that shown in *A*, stained with hematoxylin and eosin. Tuber cinereum is indicated by *tc*; supraoptic nucleus, by *son*.

phosphate is not significantly greater than in other regions of the central nervous system. Nor is it greater in the posterior and lateral nucleus of the corpus mamillare. The medial nucleus, on the other hand, concentrates sometimes slightly more P^{32}; this increase is probably not significant.

Radioautography of microscopic slides of the hypothalamic area (Fig. 7), as well as isolation and direct determination of the radioactivity of the supraoptic nucleus, shows the same increased amount of tracer in this cell group as in the adjacent, lateral part of the tuber cinereum. The P^{32} content of the optic tract is

about 30% less. The paraventricular nucleus, on the other hand, does not concentrate more of the tracer than the usual gray matter of the brain.

Determinations of the total phosphate content of various parts of the hypothalamus and of the tuber cinereum reveal the same amount of phosphate everywhere (250 to 280 mg. per 100 gm.); consequently, there is no discrepancy between data given in total counts and data converted into specific activity.

COMMENT

Borell and Örström [8] were the first to point out that the phosphate of the anterior and posterior lobes of the hypophysis in the rat interchanges with labeled phosphate (administered by intraperitoneal injection) at a much more rapid rate than does the phosphate elsewhere in the brain. They found that within the first hour after injection of P^{32} the specific activity of the pituitary gland and that of the blood (and of the choroid plexus) were of the same order of magnitude, whereas the activity of the nervous system proper lagged far behind them. It has already been demonstrated (Bakay and Lindberg,[5] Bakay [1]) that the slow accumulation of P^{32} in the brain is the consequence of a barrier function between the blood and the central nervous system and is not based upon lack of "affinity" of the brain for this tracer. The pituitary, on the other hand, as well as the pineal gland (Borell and Örström [8]) behaves like other, nonprotected organs.

It is interesting that P^{32} is concentrated equally in the anterior and in the posterior lobe of the pituitary gland. This phenomenon would be hard to explain if the deposition of the tracer were based on the histologic structure of these tissues. Aside from the difference in their endocrine functions, there is hardly any similarity between the dense parenchyma of the anterior lobe and the loose glial network of the posterior lobe. The total phosphorus contents of the two lobes are similar, although the posterior lobe seems to contain somewhat more. They have another factor in common, however; and this is their blood supply. The capillaries of the adenohypophysis do not differ from capillaries of other endocrine organs. The neurohypophysis, although much more similar in structure to the central nervous system, possesses a capillary network which differs fundamentally from that of the nervous tissue proper: It is more permeable for acid dyes, does not contain perivascular glia membrane, and the walls of its vessels are fortified with a special and dense argyrophile connective tissue layer (Spatz,[9] Nowakowski [10]). It is logical to assume that the equality of P^{32} distribution in the two lobes is a consequence of a similar capillary permeability.

Without going into the details of the special portal system and blood supply of the hypophysis, let us review the findings of Wislocki and King,[11] who established that in rabbits, cats, and monkeys the blood is supplied to the anterior and posterior

8. Borell, U., and Örström, A.: Metabolism in Different Parts of the Brain, Especially in the Epiphysis, Measured with Radioactive Phosphorus, Acta physiol. Scandinav. **10**:231-242, 1945.

9. Spatz, H.: Neues über die Verknüpfung von Hypophyse und Hypothalamus, mit besonderer Berücksichtigung der Regulation sexueller Leistungen, Acta neuroveg. **3**:5-49, 1951.

10. Nowakowski, H.: Infundibulum und Tuber cinereum der Katze, Deutsche Ztschr. Nervenh. **165**:261-340, 1951.

11. Wislocki, G. B., and King, L. S.: Permeability of the Hypophysis and Hypothalamus to Vital Dyes, with a Study of the Hypophyseal Vascular Supply, Am. J. Anat. **58**:421-472, 1936.

lobes via parallel vessels from above and that actually there is very little capillary communication between the two lobes through the pars intermedia. In man the anterior lobe is supplied by the superior hypophyseal arteries, derived from the internal carotid arteries and the posterior communicating arteries; the inferior hypophyseal arteries, which arise from the internal carotid arteries in the cavernous sinuses, supply the neural (posterior) lobe. Thus, the blood supply of one lobe is essentially independent of that of the other (Wislocki [12]). Stevens,[13] who pointed out, also, that the blood supply of the intermediate lobe is very poor, found the total observed length of capillaries in 100 cu. μ of fresh cat hypophysis to average 936 μ in the anterior lobe and 698 μ in the posterior lobe, but only 70 μ in the intermediate lobe.

There is a striking similarity between our findings and the results of the beautiful vital-dye experiments on various animals carried out by Wislocki and King.[11] Acid dyes intravenously injected, whether readily diffusible or colloidal, stain the hypophysis, both the epithelial and the neural parts, but do not deposit in the intermediate lobe. These authors found a large accumulation of the dye granules in the posterior lobe, explaining it not only by the great vascularity of that area but also by the "open texture" of the neurohypophysis. It was thought that the inherent character of this tissue permits an easy diffusion of dissolved substances leaving the blood vessels. This might be true for the larger molecules of dyes, but ions like P^{32} probably enter dense cellular or loose tissues with equal ease and therefore concentrate in the anterior and the posterior lobe without discrimination.

As one goes higher along the pituitary stalk, one finds the P^{32} concentration diminishing, and in the tuber cinereum it is only about 50% of the highest activity of the pituitary gland. Yet even these counts are many times higher than those of the white matter. Borell and Örström [8] found, after parenteral injection of P^{32}, somewhat increased specific activity in the anterior part of the tuber cinereum of rats. This phenomenon was also observed and described by Roeder [6] in dogs and guinea pigs.

According to vital-dye studies of Wislocki and King,[11] the last deposits of acid-dye granules were found in the infundibulum and its integral part on the base of the hypothalamus, the eminentia saccularis. There were still a few granules in a collection of a few small ganglion cells between the infundibulum and the optic chiasm, but beyond that all coloration stopped. Neither the tuber cinereum nor any of the recognized hypothalamic nuclei stained. There is no doubt that the blood-brain barrier increases gradually as one goes higher cranially and posteriorly into the hypothalamus. Beyond the limit of dye permeability, however, there is still a zone of increased P^{32} concentration, involving mainly the tuber cinereum. The high concentration of P^{32} in the tuber cinereum and the rapid accumulation of the tracer in this region, followed by a gradual decrease with time, suggests a local increase in the permeability of the blood-brain barrier. Even more, it suggests that with respect to their phosphate metabolism these parts of the hypothalamus are very

12. Wislocki, G. B.: Vascular Supply of the Hypophysis Cerebri of the Rhesus Monkey and Man, A. Res. Nerv. & Ment. Dis., Proc. (1936) **17**:48-69, 1938.

13. Stevens, H. M.: A Study of the Vascularity of the Pituitary Body in the Cat, Anat. Rec. **67**:377-394, 1937.

similar to the hypophysis and to other endocrine glands and differ essentially from the rest of the central nervous system.

Some other isotopes also have the tendency to concentrate in large amounts in these regions of the brain. Radioactive bromine (Br^{82}), after intraperitoneal injection in rabbits, deposits chiefly in the hypophysis and in the hypothalamus; on the other hand, very little of the tracer is seen in the rest of the brain, except for the pineal gland and the area postrema (Gruner, Sung, Tubiana and Segarra [14]). Radioactive *l*-thyroxine concentrates in the posterior lobe of the pituitary gland, but the tuber cinereum and the anterior lobe also show a higher activity than the central nervous system. Jensen and Clark [15] stated the opinion, therefore, that the neurohypophysis may be regulatory in the production of thyrotropic hormone because of its apparent affinity for *l*-thyroxine (the affinity for radioactive iodine, I^{131}, was not significant). Yet it still has to be ruled out that the concentration in the hypophysis and hypothalamus is not caused by the increased permeability of the blood-brain barrier alone. Also, *l*-thyroxine accumulates to a larger extent in the gray matter of the cortex and nuclei of the central nervous system, just as P^{32} does.

The capillary injections and measurements of Finley [16] in monkeys and of Craigie [17] in rats revealed an abundant vascular supply to the supraoptic and paraventricular nuclei. In monkeys and, presumably, in man, the nucleus supraopticus, "this extremely interesting group of densely packed nerve cells with their very special structure, is supplied by the richest capillary bed of any nucleus or group of nerve cells within the central nervous system" (Finley [16]). Its supply averaged 2,550 mm. of capillaries per cubic millimeter of tissue, as compared with 1,300 mm. for the paraventricular nucleus, 1,150 mm. for the nucleus tuberis lateralis, 1,075 mm. for the medial mamillary nucleus and 300 to 400 mm. for the other hypothalamic nuclei. Vital-dye experiments, possibly not sensitive enough, failed, however, to detect the presence of granules in these specific nuclei after intravenous administration of the dye.

As far as the supraoptic nucleus is concerned, somewhat increased deposits of P^{32} have been found in that region by direct determination of the radioactivity, as well as by radioautography of microscopic slides. The concentration of the tracer was not greater in this nucleus than in the neighboring areas of the lateral portion of the tuber cinereum, however, although it was definitely greater than in the closely related optic tract. It could be objected that the higher counts in this nucleus are due to the blood pooled in its abundant vascular bed, but this objection can be ruled out by the fact that in the overwhelming majority of cases the P^{32} level of the blood was already diminished to such an extent that it could hardly interfere with the determinations. Rather, it would seem that the supraoptic nucleus, notwithstanding its large vascular bed, lies in an area where the permeability of the blood-brain barrier is increased, together with the less vascular nuclei of the tuber cinereum.

14. Gruner, J.; Sung, S. S.; Tubiana, M., and Segarra, J.: Le mouvement du radiobrome dans le système nerveux du lapin, Compt. rend. Soc. biol. **145**:203-206, 1951.

15. Jensen, J. M., and Clark, D. E.: Localization of Radioactive *l*-Thyroxine in the Neurohypophysis, J. Lab. & Clin. Med. **38**:663-670, 1951.

16. Finley, K. H.: Angio-Architecture of the Hypothalamus and Its Peculiarities, A. Res. Nerv. & Ment. Dis., Proc. (1939) **20**:286-310, 1940.

17. Craigie, E. H.: Measurements of Vascularity in Some Hypothalamic Nuclei of the Albino Rat, A. Res. Nerv. & Ment. Dis., Proc. (1939) **20**:310-323, 1940.

This theory is supported by the behavior of the paraventricular nucleus, which, being more cranially situated, falls in an area of decreased permeability and contains much less P^{32}, certainly not more than the surrounding area, in spite of its large blood supply. This finding also demonstrates that abundant circulation of blood throughout a specific and well-circumscribed area of the brain does not necessarily mean that the permeability of the blood-brain barrier is also greater than that in less vascular regions. It can be greater, of course, as in the area postrema, where the large capillary network is definitely more permeable (according to experiments of Wislocki and Putnam [18] with vital dyes, and those of Tubiana, Gruner, Olomucki, and Sung [19] with Br^{82}).

How, then, can the peculiar behavior of the tuber cinereum be explained? One important factor in the exchange of labeled and unlabeled phosphate in a tissue is the total amount of exchangeable phosphate. There is no significant difference in this respect between the tuber and other parts of the brain. Another important factor may be increased vascularity and/or increased vascular permeability (increased permeability or complete absence of the blood-brain barrier). This possibility was mentioned by Stern and Marshall [20] as a likely source of increased P^{32} concentration in destroyed or damaged brain tissue. Yet the example of the paraventricular nucleus (and that of the supraoptic nucleus, to some extent) suggests that increased vascularity alone does not necessarily result in higher ion uptake by the tissues. In this connection, one comes to the often-discussed problem of correlation between vascularity and metabolism in the central nervous system. Himwich [21] pointed out that vascular reactions are the result, not the cause, of cerebral activity, and that larger blood supply is merely a physiologic adaptation to the acceleration of metabolism. Many data accumulated by Craigie [22] and by Wolff and associates [23] strongly suggest a congruity between cerebral metabolism and capillary population. The work of Wolff and associates [23] did not reveal a striking relationship between the extent of vascularity and the number of nerve cells but, rather, showed a correlation between the degree of vascularity and the number of synapses. The supraoptic and paraventricular nuclei were considered as exceptions to this theory. According to the experimental and clinical findings of Spatz,[9] the parvocellular region of the tuber cinereum belongs to the "hypothalamic sexual center," which is essential for the

18. Wislocki, G. B., and Putnam, T. J.: Note on the Anatomy of the Area Postrema, Anat. Rec. **18**:281-285, 1920.

19. Tubiana, M.; Gruner, J.; Olomucki, M., and Sung, S. S.: Le mouvement du radiobrome dans le système nerveux du lapin: Étude après perfusion, Compt. rend. Soc. biol. **145**: 1009-1011, 1951.

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maturing of the gonads in mammals. Similar observations were made earlier by Dey, Fisher, Berry, and Ranson,[24] who reported that in female guinea pigs lesions in the hypothalamus between the optic chiasm and the attachment of the infundibular stalk produced sterility and disturbances in reproductive functions. This finding explains why mating was found very substantially to increase the P^{32} uptake by the tuber cinereum of rabbits (Borell, Westman, and Örström [25]). It is possible that this high uptake of P^{32}, and probably of other ions, is the result of the role of this area in endocrine functions, the structures being characterized not only by a rich capillary network but also by an increase in the permeability of its barrier. It is of less importance in this respect whether the barrier is identical with the capillary wall or not.

SUMMARY

The concentration of P^{32} in various parts of the hypophysis and hypothalamus was determined in 12 human subjects, from six hours to three weeks after a single intravenous injection of the isotope.

A larger deposit of P^{32} was found in the pituitary gland, infundibulum, and tuber cinereum than in other parts of the brain. Other hypothalamic regions did not differ significantly from the central nervous system.

There was no significant difference in the phosphate uptake of the anterior and that of the posterior lobe of the pituitary gland in the majority of cases. The intermediate lobe, if present, concentrated less P^{32}.

Time curves for P^{32} concentrations of various areas indicate a fundamental difference between the uptake of phosphates by the hypophysis (and other parenchymatous organs) and that of the brain. The tuber cinereum follows the former pattern.

The role of the tuber cinereum and that of the supraoptic and paraventricular nuclei are discussed with special regard to the correlation between vascularity and metabolism and to the permeability of the blood-brain barrier.

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PROTEIN CONTENT OF SPINAL FLUID IN DIABETES MELLITUS

Report on One Hundred Cases

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ELEVATION of the total-protein content of the cerebrospinal fluid has been noted in several disorders of metabolism and in diseases in which the metabolism is disturbed. Thus, the protein value of the spinal fluid has been found increased in myxedema (Thompson and associates [1]), chronic nephritis (Lyttle and Rosenberg [2]), uremia (Madonick, Berke, and Schiffer [3]), and Cushing's syndrome (Trethowan and Cobb [4]). Although an increase in the protein content of the spinal fluid of diabetic patients with peripheral neuropathy has been reported fairly frequently (Root and Rogers,[5] Jordan,[6] Rundles,[7] Epstein [8]), information regarding the protein concentration of the spinal fluid in diabetic patients without clinical neurologic involvement is meager. Mestrezat [9] and Levinson [10] stated that the spinal-fluid protein value is normal. Lochelongue [11] found increased protein in the spinal fluid in diabetes mellitus. Eskuchen [12] indicated that there may be a slight increase in

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11. Lochelongue, I.: Le liquide céphalo-rachidien et ses anomalies, Paris, A. Maloine & Fils, 1918, p. 237.

12. Eskuchen, K.: Die Lumbalpunktion: Technik der Lumbalpunktion, Berlin, Urban & Schwarzenberg, 1919, p. 162.

globulin of the spinal fluid in diabetic coma, and Meyer [13] mentioned the occurrence of a slightly increased protein concentration in impending diabetic coma. Merritt and Fremont-Smith [14] wrote:

> In diabetes mellitus the cerebrospinal fluid is normal except for a high sugar content. Occasionally, the fluids may have a slightly elevated protein content, especially in the cases complicated by neuritis or in the cases with a low basal metabolic rate.

All the aforementioned investigators did not indicate the number of patients examined or give the protein values. Bruno [15] reported the protein value to be normal or slightly elevated in psychoses with diabetes; the psychoses were not described, and the presence or absence of other possible contributing conditions was not stated. Of Alpers' [16] 19 cases of diabetes mellitus, the protein content was normal in 10 and slightly increased in 9; in 1 case the protein was 90 mg. per 100 cc. Root [17] determined the spinal-fluid protein concentrations in 84 cases of diabetic neuropathy and in 53 cases of diabetes with surgical infections of the feet; in 87% of the former group and in 43% of the latter group protein values of 50 mg. or over per 100 cc. were observed.

PRESENT STUDY

In order to determine whether there is an alteration in the protein content of the spinal fluid in diabetes mellitus, especially in patients with no neurologic signs, we examined 100 diabetic patients neurologically. Of the 100 patients, 80 had no neurologic signs or symptoms, and 20 had neurologic signs. Fifteen had hemiplegias due to hypertension or atherosclerosis; the diabetes was, at most, an indirect factor by its tendency to cause earlier atherosclerosis; 4 had peripheral neuropathy and 1 had myelopathy due to the diabetes. Conditions in the diabetic patients which could increase the spinal-fluid protein, such as myxedema,[1] nephritis,[2] uremia,[3] Cushing's syndrome,[4] or multiple myeloma [18]; a history of syphilis or positive serological reactions for syphilis of the blood or the spinal fluid, or a history of, or positive reaction in the skin test for, lymphogranuloma venereum [19] resulted in exclusion of these patients from the series. The spinal-fluid cell count and protein value, as well as blood sugar values, were determined in each case. Serum proteins, in specimens drawn at the same time that the spinal puncture was performed, after a night's fast, were also estimated in 45 of the cases. A modification of Andersch and Gibson's [20] method was used for the protein determinations. Although 40 mg. per 100 cc. is considered as the highest range of the normal in this procedure, we regarded values below 50 mg. per 100 cc. as still within normal limits.

13. Meyer, H. H.: Der Liquor: Untersuchung und Diagnostik, Berlin, Springer-Verlag, 1949, p. 172.

14. Merritt, H. H., and Fremont-Smith, F.: The Cerebrospinal Fluid, Philadelphia, W. B. Saunders Company, 1938, p. 193.

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18. Degenhardt, D., and Sheehan, D.: Multiple Myeloma, Brit. M. J. **2**:1016, 1949.

19. Finberg, L.; Lord, R. E., and Cenac, M. T.: Characteristics of Cerebrospinal Fluid in Lymphogranuloma Venereum, J. Ven. Dis. Inform. **30**:291, 1949.

20. Andersch, M., and Gibson, R. B.: Colorimetric Determination of Plasma Proteins, J. Lab. & Clin. Med. **18**:816, 1933.

The series comprised 68 females and 32 males. The age distribution, according to decades is shown in the accompanying tabulation:

Age decade	0-9	10-19	20-29	30-39	40-49	50-59	60-69	70-79
Males	..	..	..	..	7	12	14	5
Females	..	2	..	..	5	16	26	13

The duration of the diabetes varied from 2 months to 24 years.

Our results show that only 5 of the 100 diabetic patients had protein concentrations of the spinal fluid of 50 mg. or over per 100 cc. These five patients had neurologic signs; one of them, a patient with recent hemiplegia, had a protein value of 52 mg. per 100 cc.; the other four, all with peripheral neuropathy, had protein values of 52, 65, 67, and 210 mg. respectively, per 100 cc. The duration of the diabetes for the non-neurologic diabetic patients was 98.5 months, and that for the five with increased spinal fluid protein was 93.6 months. This difference is not significant. There was no definite relation between the values for the spinal-fluid protein and the duration of the diabetes. However, there was a suggestive relation between the spinal-fluid protein and the severity or difficulty in managing the diabetes. The patients with increased spinal-fluid protein required somewhat more insulin, and their diabetes was somewhat more difficult to control. This observation is in agreement with Kerr, Brown, and Kalant's [21] conclusion that peripheral neuropathy and other complications develop more commonly when the diabetes is poorly controlled, or is not controlled at all. There was no clear-cut relation of the blood sugar to the spinal-fluid protein. Thus, two patients with blood-sugar concentrations of 540 and 400 mg. per 100 cc. had spinal-fluid proteins of 35 and 22 mg. per 100 cc., respectively. No correlation was observed between the spinal-fluid and serum protein values in the 45 instances in which these determinations were done. Of the 100 spinal fluids, only 1 had a white blood cell count of 5 polymorphonuclear leucocytes per cubic millimeter; this patient had no neurologic signs.

SUMMARY AND CONCLUSIONS

Since the spinal-fluid protein content is at times increased in various diseases of metabolism or disorders in which the metabolism is disturbed, and since diabetes mellitus is an excellent example of a metabolic disorder, cell counts and total-protein determinations were made on the spinal fluids of 100 diabetic patients. Of the 100 patients, 80 had no objective signs of neurologic involvement. Of 20 with neurologic signs, 15 had hemiplegia; 4, peripheral neuropathy, and 1, myelopathy on a diabetic basis.

The spinal fluid of only one patient had a white cell count of 5 polymorphonuclear leucocytes per cubic millimeter; this patient had no neurologic signs.

The spinal-fluid protein value was 50 mg. or over per 100 cc. in only 5 of the 100 patients; 4 of the 5 had peripheral neuropathy, and the fifth had a recent hemiplegia.

Although there was no relation between the increase in the spinal-fluid protein and the duration of the diabetes, there was a suggestive relation between increase in the spinal-fluid protein and the severity or the difficulty in control of the diabetes.

21. Kerr, R. B.; Brown, G. D., and Kalant, N.: Follow-Up Study of Juvenile Diabetics, Canad. M. A. J. **66**:97, 1952.

No relationship between the spinal-fluid protein and the blood sugar levels was demonstrated.

No relation of the spinal fluid to the serum protein concentrations was observed in the 45 patients so tested.

Our results show that an increase in the cerebrospinal-fluid protein is found in diabetes mellitus only when neurologic complications are present; the commonest complication with an increase in the spinal-fluid protein concentration was peripheral neuropathy.

Miss R. S. Glauberman, B.S., of the Laboratory Division, did the chemical analyses, and Dr. L. Ebin performed 15 of the lumbar punctures.

SERUM CHOLINESTERASE ACTIVITY IN MENTAL DISEASE

Effect of Shock Therapy

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AND
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A CONSIDERABLE body of biochemical, pharmacologic, and physiologic data suggests an important, if not major, role for the acetylcholinesterase-acetylcholine system in the transmission of the nerve impulse.[1] This has apparently prompted a number of investigations into the variations in serum cholinesterase activity in relation to mental diseases characterized by changes in mood or mentation,[2] as well as studies on the effect of therapy of mental disorders on the serum enzyme level [3] and observations on the effect of cholinesterase inhibitors on mental activity and emotional status.[4] Although the reported results are at some variance with one another, it was decided, in view of a claim of a significant elevation in serum cholinesterase activity in anxiety states and a significant depression of its activity in schizophrenia,[2a] to reinvestigate this problem. A recently developed colorimetric method with a fairly high degree of accuracy and reproducibility, based on a substrate having absolute specificity for serum cholinesterase, has been employed throughout.[5]

MATERIALS AND METHODS

Serum cholinesterase and serum esterase activities, measured by the ability of the patient's serum to hydrolyze β-carbonaphthoxycholine iodide and β-naphthylacetate,[5] respectively, were determined one or more times in each of 60 patients under observation in a mental hospital. A series of 10 patients subjected to electroshock therapy during the course of hospitalization were studied in like manner, with venous-blood samples taken before shock and 1 minute, 10 minutes, and 4 hours after electroshock. The blood was allowed to clot, and the serum was stored in the cold (4 C.) until the determinations were performed. It has been shown previously that storage under these conditions does not affect the measured activity.[5]

From the Laboratory of Clinical Physiology, McLean Hospital, Waverley, Mass.; the Yamins Surgical Research Laboratory, Beth Israel Hospital, Boston, and the Department of Medicine, Harvard Medical School.

1. Quastel, J. H., in Nerve Impulse, New York, Josiah Macy Jr. Foundation, 1951, Chap. 2.

2. (*a*) Randall, L. O.: J. Lab. & Clin. Med. **25**:1025, 1940. (*b*) McGeorge, M.: Lancet **1**:69, 1937. (*c*) Early, D. F.; Hemphill, R. E.; Reiss, M., and Brummel, E.: Biochem. J. **45**: 552, 1949.

3. (*a*) Tod, H., and Jones, M. S.: Edinburgh M. J. **44**:46, 1937. (*b*) Randall, L. O., and Jellinek, E. M.: Endocrinology **25**:278, 1939.

4. Rowntree, D. W.; Nevin, S., and Wilson, A.: J. Neurol., Neurosurg. & Psychiat. **13**: 47, 1950.

5. Ravin, H. A., Tsou, K-C., and Seligman, A. M.: J. Biol. Chem. **191**:843, 1951.

OBSERVATIONS

Serum cholinesterase activity in patients exhibiting manifest depression fell into a range of 15 to 60 units [6] per 100 cc. of serum, exactly coinciding with the range of variation found earlier in a series of healthy blood donors.[5] The mean value for serum cholinesterase for the depressed group, however, was 44.8 units per 100 cc., as compared with a mean value of 36.7 units per 100 cc. in concurrent determina-

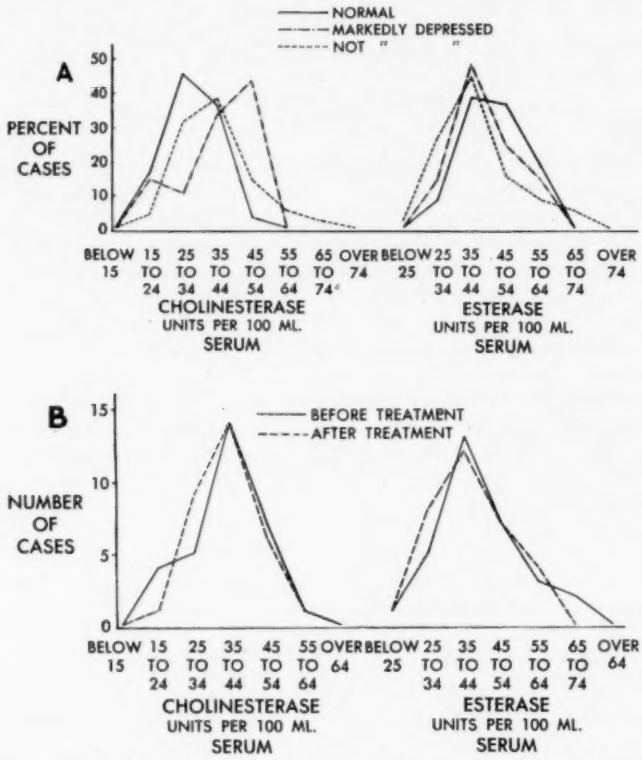

Fig. 1.—*A*, distribution of serum cholinesterase and serum esterase concentrations on initial determination on each patient prior to any therapy. Distribution of enzyme concentration obtained in healthy blood donors one year earlier (solid line) is included for comparison.

B, distribution of serum enzyme concentrations before and after therapy.

tions on a control group of nondepressed patients, and with a mean value of 32.9 units per 100 cc. for the original healthy, control series (Chart 1*A*). Statistical evaluation of the data reveals that the differences in serum cholinesterase activity in the depressed patients, on comparison with the values for nondepressed patients,

6. "One unit of serum cholinesterase activity is defined as that amount of enzyme which liberates 10 mg. of β-naphthol per hour from carbonaphthoxycholine iodide under the standard conditions of the test (pH 7.4, temperature of 37 C., substrate concentration 1.2 X 10^{-4} M)."[5]

are not significant ($t = 1.86$; $p > 0.05$). Although statistical analysis suggests that depressed patients may have a significant elevation in serum cholinesterase activity over the healthy, control subjects ($t = 2.74$; $p < 0.02$), the enzyme activities in the latter group had been measured one year earlier, so that unrecognized variables that may influence the estimation of activity were not adequately controlled for this comparison.

The serum esterase activity, which is a measure of serum cholinesterase plus a number of unidentified esterolytic enzymes present in human serum, was not significantly different from that for the control series (Chart 1*A*).

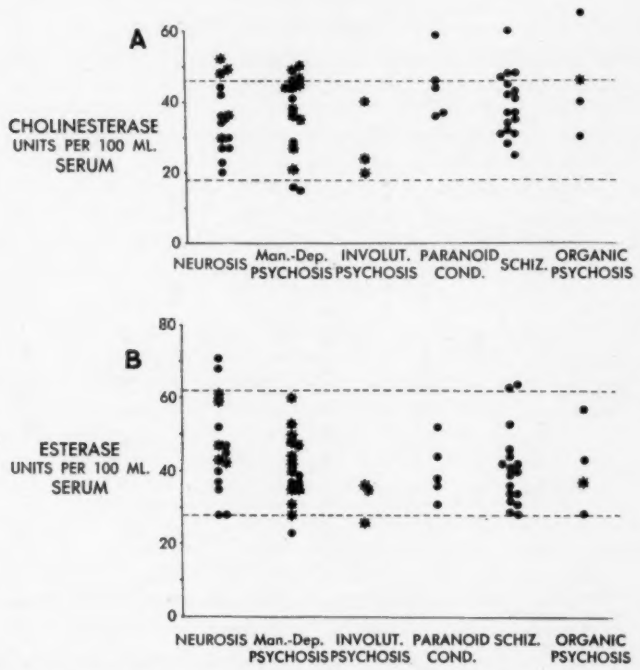

Fig. 2.—*A*, distribution of serum cholinesterase levels in each category of primary psychiatric diagnoses. Crenelated points represent values obtained after electroshock therapy. Note tendency to high normal values in schizophrenia.

B, distribution of serum esterase levels in each category of primary psychiatric diagnoses. Crenelated points represent values obtained after therapy.

Comparison of serum cholinesterase and serum esterase activities before treatment and after therapy for periods of up to four weeks revealed no significant changes incident to therapy. Some of these patients showed marked clinical improvement during this time; others no change at all (Chart 1*B*).

Division of the cases into six major diagnostic categories, viz., psychoneurosis, manic-depressive psychosis, involutional psychosis, paranoid state, schizophrenia, and organic psychosis, shows no striking differences in any of the subdivisions, with

the possible exception of the small group of schizophrenic patients, who had a tendency to high-normal serum cholinesterase levels (Chart 2*A*) and low-normal esterase levels (Chart 2*B*).

After electroshock therapy there were minor changes in the serum cholinesterase and serum esterase activities, most patients showing a transient increase in the concentration of both enzymes (Chart 3). The average rise in serum cholinesterase levels over preshock values was 4.0 units per 100 cc. at 1 minute, 4.9 units per 100 cc. at 10 minutes, and 1.5 units per 100 cc. after 4 hours. Comparable figures for serum esterase were + 5.7 units per 100 cc. at 1 minute, 0.5 unit per 100 cc. at 10 minutes, and no change from preshock levels at 4 hours.

COMMENT

It is not generally appreciated that the cholinesterase of human serum is an entirely different enzyme from that found throughout most of the nervous system.[7]

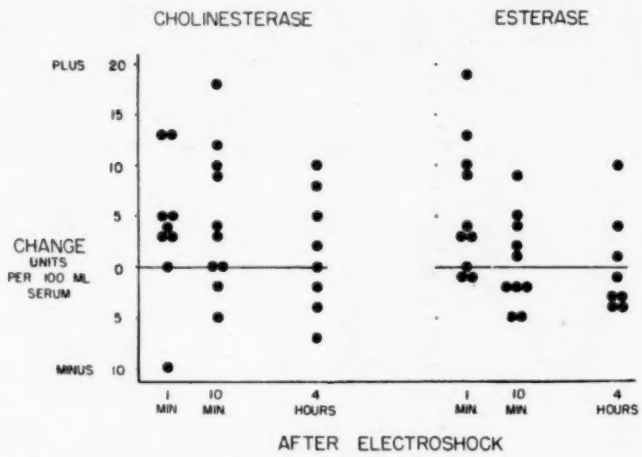

Fig. 3.—Changes in serum cholinesterase and serum esterase values, in relation to pretreatment values, incident upon electroshock therapy.

Serum cholinesterase is thought to be produced primarily by the liver,[8] and the concentration of the circulating enzyme may be correlated very well with the status of hepatic function.[9] The pancreas and adrenal medulla are also known to be sites of relatively high serum cholinesterase activity, but their contribution to the circulating enzyme, if any, is not known.

7. The acetylcholinesterase (synonyms, "true cholinesterase," "specific cholinesterase," Type e, Type I) of the central nervous system differs from the cholinesterase (synonyms, "pseudocholinesterase, nonspecific cholinesterase, Type s, Type II) of human serum in that it is able to hydrolyze methacholine (acetyl-β-methylcholine), but not benzoylcholine, while the reverse is true for the latter enzyme (Mendel, B., and Rudney, H.: Biochem. J. **37**:59, 1943).

8. Sawyer, C. H., and Everett, J. W.: Am. J. Physiol. **148**:675, 1947. Wescoe, W. C.; Hunt, C. C.; Riker, W. F., and Litt, I. C.: Ibid. **149**:549, 1947.

9. Vorhaus, L. J., II; Scudamore, H. H., and Kark, R. M.: Am. J. M. Sc. **221**:140, 1951.

Within the nervous system, serum cholinesterase has been demonstrated histochemically in the ganglion cells and synaptic junctions of the parasympathetic outflow.[10] Although it is interesting to speculate that the level of serum cholinesterase might also reflect the activity of this portion of the nervous system, there is no evidence for secretion of cholinesterase upon stimulation of these pathways.

The present study reveals no significant differences in the concentration of serum cholinesterase in mentally depressed patients on comparison with that in nondepressed patients. The lack of correlation between serum cholinesterase activity and the mental state of the patient is not surprising in view of evidence for the liver as the major source of the circulating enzyme.

These results are in agreement with those of McGeorge [2b] and of Butt and associates,[11] who found no significant variation from the normal in "chronic nervous exhaustion" or in "neurosis." Randall [2a] found slightly low, but not statistically significant, values for serum cholinesterase in schizophrenia. Although Tod and Jones [3a] found no significant variation from the normal in hysteria, mania, involutional melancholia, or paranoia, they reported a significant elevation of serum cholinesterase in anxiety states and in catatonic stupor. They claimed a significant lowering of serum cholinesterase levels in epilepsy and in schizophrenia and a tendency (not statistically significant) to low values in depressive psychosis. There was no correlation, however, between the depth of depression and the serum enzyme activity.[3a]

Early and associates,[2c] using methacholine (acetyl-β-methylcholine) and acetylcholine to distinguish between acetylcholinesterase and serum cholinesterase, reported a significant increase in circulating acetylcholinesterase in a small series of psychotic patients as compared with that in normal controls. The measured activity against methacholine, however, was extremely low in all cases and must have been subject to a rather large experimental error in determination. No correlation could be found between "true" and "pseudo" cholinesterase levels.

The transient slight rise in serum cholinesterase activity noted here after shock therapy may be related to the hemoconcentration which has been shown to occur regularly after such treatment.[12] A rise of similar duration and equivalent amount was found by Early and associates,[2c] using acetylcholine as the substrate for measuring the enzyme. Randall [2a] reported a rise following insulin shock therapy, which he attributed only partially to hemoconcentration.

Rowntree and associates [4] recently reported that diisopropyl fluorophosphate produced a marked lowering of serum cholinesterase activity and that concomitantly it produced alteration in the electroencephalographic pattern, increased depression in manic-depressive psychosis, mild depression in normal subjects, and increased severity of psychosis in schizophrenic patients. These mood changes, however,

10. Ravin and associates.[5] Koelle, G. B.: J. Pharmacol. & Exper. Therapy. **100**:158, 1950. Gomori, G.: Proc. Soc. Exper. Biol. & Med. **68**:354, 1948.

11. Butt, H. R.; Comfort, M. W.; Dry, T. J., and Osterberg, A. E.: J. Lab. & Clin. Med. **27**:649, 1941.

12. Altschule, M. D.; Cram, J. E., and Tillotson, K. J.: Arch. Neurol. & Psychiat. **59**:29, 1948.

cannot be attributed to the measured diminution in serum cholinesterase, even though they may be well correlated with one another, since this agent is an equally potent inhibitor of the acetylcholinesterase of the central nervous system.

SUMMARY

Serum cholinesterase activity determined by a sensitive and specific colorimetric method could not be correlated with the psychiatric diagnosis, response to therapy, or presence or absence of marked overt depression in a series of 60 hospitalized psychiatric patients. A transient rise in serum cholinesterase activity occurs in a majority of patients subjected to electroshock therapy and appears to be largely related to transient hemoconcentration. A brief review of the nature and probable origin of the serum cholinesterase suggests that the level of the circulating enzyme could bear no direct relation to the mental state, alleged correlations in some series and pharmacologic studies notwithstanding.

EFFECT OF SERIES OF ELECTRIC SHOCK TREATMENTS ON CEREBRAL BLOOD FLOW AND METABOLISM

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SINCE the introduction of electric shock therapy, there has been much debate as to the effect of the treatment on the human brain. Pathological studies on animals [1] have, in general, failed to show any histological changes in the brain following a series of therapeutic electric shock treatments. Kety and associates,[2] in studying a series of patients 10 to 20 minutes after one treatment, demonstrated a pronounced drop in cerebral blood flow with a less pronounced drop in cerebral metabolism. These changes, however, were associated with a drop in the pH of the blood and in carbon dioxide tension and were probably, at least in part, secondary to the marked changes in body metabolism brought about by the convulsion.

It has long been known that temporary disturbances in memory and orientation frequently occur in patients undergoing electric shock therapy. These changes are variable and are much severer in some patients than in others. Since these disturbances are usually observed after several treatments, it was believed that a study of cerebral blood flow and metabolism was indicated after the patient had received a therapeutic series of treatments and was in a relatively normal metabolic state.

METHOD

Twenty-one physically normal, adult psychotic patients were selected for this series. Except for mild hypertension in several of the older patients, no physical disease was observed in the

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Instructor in Psychiatry and Research Fellow in Medicine, Duke University School of Medicine (Dr. Wilson); Fellow of the American Heart Association and Instructor in Medicine, Duke University School of Medicine (Dr. Schieve).

1. Seikert, R.; Williams, S., and Windle, W.: Histologic Studies of Brains of Monkeys After Experimental Electric Shock, Arch. Neurol. & Psychiat. **63**:79-86 (Jan.) 1950. Alexander, L., and Lowenbach, H.: Experimental Studies on Electro-Shock Treatment: Intracerebral Vascular Reaction as Indicator of Path of Current and Threshold of Early Changes Within Brain Tissue, J. Neuropath. & Exper. Neurol. **3**:139-171 (April) 1944.

2. Kety, S.; Woodford, R.; Hormel, M.; Freyhan, F.; Appel, K., and Schmidt, C.: Cerebral Blood Flow and Metabolism in Schizophrenia: Effects of Barbiturate Semi-Narcosis, Insulin Coma and Electro-Shock, Am. J. Psychiat. **104**:765-770 (June) 1948.

entire series. The hemoglobin level of four patients was between 10 and 12 gm. per 100 cc.; that of the remainder was above 12 gm. per 100 cc. The average age for the group was 45, with a range of 24 to 68. For 10 patients the diagnosis was depression; for 9, schizophrenia; for 1, delirium, and for 1, presenile psychosis with depression. Electric shock treatments were given to 13 patients with the Liberson brief stimulus apparatus, and 9 patients were treated with the Rahm electroshock unit. Electric shock therapy was given in all cases until the patient had recovered from his psychosis or until the patient's clinical course indicated that further treatment would be of no value to the patient.

The cerebral blood flow was determined by the nitrous-oxide technique described by Kety [3] as modified by Scheinberg and Stead.[4] This method measures the cerebral blood flow per 100 gm. of brain tissue. Arterial-cerebral venous blood oxygen differences were determined by the method of Hickam and Frayser,[5] in which are used the average difference between one arterial and one venous sample drawn before the blood flow, and a second arterial and a second venous sample drawn after the blood flow.

Blood glucose levels were determined by Nelson's modification of Somogyi's method.[6] Arterial-cerebral venous blood glucose differences were calculated from the values obtained from four arterial and four venous samples. Two arterial and two venous samples were obtained before the blood flow was begun. The remaining samples were obtained after the termination of the blood flow. Blood pressure readings were made by the auscultatory method, a sphygmomanometer being used with the arm held at heart level. The mean arterial blood pressure was calculated by adding one-third of the pulse pressure to the diastolic pressure. The cerebral metabolic rates of oxygen and glucose consumption, in cubic centimeters of oxygen and milligrams of glucose per 100 gm. of brain per minute, were calculated by multiplying the cerebral blood flow by the respective arterial-cerebral venous blood oxygen and glucose differences.

In all cases but one a control blood-flow determination was done prior to the institution of therapy. Patient 5 received three treatments before the control study was done. Patient 7 had been given a course of treatments six months prior to the beginning of the study. After the institution of therapy, all patients were followed closely and observed for evidence of confusion, as well as clinical signs of improvement. Five patients were studied during therapy, after they had received an average of five electric shock treatments. After the termination of therapy, all the patients were studied within a period of one to three days. The average number of treatments received by the entire group was 10, with a range of 3 to 15.

RESULTS

Evaluation of the patients' mental status prior to the last investigation showed 10 patients recovered, 6 improved, and 5 unimproved. Four of the patients who were unimproved had a condition diagnosed as schizophrenia; the fifth, a disorder diagnosed as presenile psychosis with depression. Marked confusion was observed in four patients.

The results of the blood-flow studies are tabulated in the accompanying Table. The value before treatment for cerebral blood flow is lower, and the arteriovenous oxygen difference is greater than the corresponding values for the series of normal young men previously reported.[4]

3. Kety, S. S., and Schmidt, C. F.: Nitrous Oxide Method for Quantitative Determination of Cerebral Blood Flow in Man: Theory, Procedure and Normal Values, J. Clin. Invest. **27**:476-483 (July) 1948.

4. Scheinberg, P., and Stead, E. A., Jr.: Cerebral Blood Flow in Male Subjects as Measured by the Nitrous Oxide Technique: Normal Values for Blood Flow, Oxygen Utilization, Glucose Utilization and Peripheral Resistance, with Observations on the Effect of Tilting and Anxiety, J. Clin. Invest. **28**:1163-1171 (Sept.) 1949.

5. Hickan, J., and Frayser, R.: Spectrophotometric Determination of Blood Oxygen Content, J. Biol. Chem. **180**:457-465 (Aug.) 1949.

6. Nelson, N.: A Photometric Adaptation of the Somogyi Method for the Determination of Glucose, J. Biol. Chem. **153**:375-380 (May) 1944.

The data after treatment show considerable scatter, but the most striking finding is the lack of correlation of the degree of clinical improvement, the presence of confusion, and the cerebral blood flow and metabolism. Analysis of data for the entire group shows a trend toward reduction in cerebral oxygen metabolism which is not statistically significant ($p = > 0.05$). The blood flow is not significantly decreased ($p = > 0.3$). No significant changes in arterial-cerebral venous blood oxygen and glucose differences were noted.

Mean Values for Twenty-One Patients Treated with Electric Shock Therapy

	Before	After	p Value
Cerebral blood flow, cc. of blood/100 gm. brain/min.	56 ± 12.6*	52 ± 14.3*	>0.3
A-V oxygen blood difference, vol. %	6.8 ± 3.1	6.6 ± 1.0	...
A-V glucose blood difference, mg./100 cc.	9.6 ± 2.1†	9.3 ± 2.3†	...
Cerebral metabolic rate for O_2 cc. O_2/100 gm. brain/min.	3.7 ± .72	3.3 ± .64	>0.05
Cerebral metabolic rate for glucose, mg. glucose/100 gm. brain/min.	5.3 ± 1.47†	4.8 ± 1.57†	0.3
Mean arterial blood pressure, mm. Hg	90‡	92‡	...

* Standard deviation.
† Values obtained for 18 studies.
‡ Standard deviation not calculated.

COMMENT

It is possible that a larger series might demonstrate a significant, but slight, decrease in oxygen consumption. Even if this were so, the changes observed would be of such small magnitude as to have no clinical significance and throw no light on the mechanism for improvement from electric shock therapy or for the confusion following therapy. It is possible that the minor changes of the degree noted here are related to changes in endocrine function or changes in the nutritional state of the patient, rather than specifically to changes produced in the brain by the electric current. This impression is based on experience with other diseased states, such as myxedema, arteriosclerosis, and pernicious anemia,[7] in which minor alteration in over-all cerebral metabolism of the extent found in these patients after shock has not been associated with detectable changes in mental function. It is also possible that changes in the cortex itself are more pronounced and are not revealed by the techniques now used for measuring cerebral blood flow and metabolism.

Previous investigations have shown that changes in cortical oxygen tension and pH,[8] as well as changes in cerebral metabolism and cerebral blood flow,[2] are associated with an electrically induced convulsion. However, these changes are related to the physiological and metabolic changes that occur during the convulsion and do not aid in explaining the phenomena of improvement or confusion resulting from electric shock therapy. Pacella [9] has shown that transitory alterations in cerebral

7. Scheinberg, P.; Stead, E. A., Jr.; Brannon, E., and Warren, J.: Correlative Observations on Cerebral Metabolism and Cardiac Output in Myxedema, J. Clin. Invest. **29**:1139-1146 (Sept.) 1950. Scheinberg, P.: Cerebral Blood Flow in Vascular Disease of the Brain, with Observations on the Effect of Stellate Ganglion Block, Am. J. Med. **8**:139-147 (Feb.) 1950; Cerebral Blood Flow and Metabolism in Pernicious Anemia, Blood **6**:213-227 (March) 1951.

8. Jasper, H., and Erickson, T.: Cerebral Blood Flow and pH in Excessive Cortical Discharge Induced by Metrazol and Electrical Stimulation, J. Neurophysiol. **4**:333-347 (July) 1941.

9. Pacella, B.; Barrera, S. E., and Kalinowsky, L.: Variations in Electroencephalogram Associated with Electric Shock Therapy of Patients with Mental Disorders, Arch. Neurol. & Psychiat. **47**:367-384 (March) 1942.

electroactivity occur during the early part of a series of electric shock treatments and usually will persist after eight or more treatments. These changes, however, persist longer than clinically observed confusion and apparently are not associated with the confusion or with improvement of the patient's mental status. This study does not help to explain these changes.

The observation of Himwich and associates [10] that arterial-cerebral venous blood oxygen differences do not change significantly is corroborated by this study.

SUMMARY AND CONCLUSIONS

Cerebral blood flow and cerebral metabolic studies were done on 21 patients before and after they had received an average of 10 electric shock treatments.

No significant changes in cerebral blood flow or oxygen consumption occurred. Cerebral oxygen consumption fell from 3.7 to 3.3 cc. of oxygen per 100 gm. of brain ($p = > 0.05$).

Neither clinical improvement nor mental confusion produced by electric shock therapy is associated with changes in cerebral blood flow or cerebral metabolism as measured by present techniques.

Miss Melba Holder and Mrs. Mary Robertson gave technical assistance; Dr. James Murdoch and the medical and nursing staff of the Butner State Hospital cooperated in the making of this study.

10. Himwich, H.; Cameron, D. E.; Homburger, E., and Feldman, F.: Cerebral Metabolism in Patients with Depression, Am. J. Psychiat. **101**:453-454 (Jan.) 1945.

HEREDITARY (FAMILIAL) SPASTIC PARAPLEGIA

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SINCE 1876,[1] a heredofamilial disease has been known in which the only disturbance, or the most prominent disturbance, has been a slowly progressive weakness and spasticity of the lower extremities. Contributions by Strümpell [2] and Lorrain [3] have led writers to designate this disease by their names. By 1939, according to Price,[4] reports on 158 families presumed to have this condition had accumulated in the literature, although another writer,[5] in the same year, included in her excellent study only 74 pedigrees, with a total of 316 affected members. She added one more pedigree of familial spastic paraplegia of her own. Since that time several more families have been reported in the literature.

There exists a considerable variation of opinion about many aspects of this disease, e. g., the clinical identity of the disease, that is, whether it is really a separate syndrome or represents but one of the many possible manifestations of a common disease process; what the hereditary factors are, and difficulties in clinicopathologic correlations, and so forth. In an attempt to answer these questions, many more cases will have to be recorded, with careful clinical, laboratory, and pathologic studies. I have had the opportunity of seeing four families with this neurologic syndrome. Thirty-two persons were affected, and 12 of them have been examined. Because they represented the "pure" form of the disease, and because a study of the spinal cord and brain stem in a former clinically reported typical case was made possible, it was felt that this material should be added to the literature.

REPORT OF PEDIGREES AND CASES

Family Ze. (Fig. 1).—The original patient was G. Ze., who was of the fifth generation. He was the source of much of my information about the family, although I was able to verify and extend his data by questioning many other members of the family. His great-great-grandmother had been born in Germany. It was known in the family that this woman had been affected with the disease, although no details of her condition or its development were available. This woman

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1. Seeligmüller, A.: Sklerose der Seitenstrange des Rückenmarks bei vier Kindern derselben Familie, Deutsche med. Wchnschr. **2**:185-186, 1876.

2. Strümpell, A.: Beiträge zur Pathologie des Rückenmarks, Arch. Psychiat. **10**:676-717, 1880; Über die hereditäre spastische Spinalparalyse, Deutsche Ztschr. Nervenh. **4**:173-183, 1893.

3. Lorrain, M.: Contribution à l'étude de la paraplégie spasmodique familiale, Paris, G. Steinheil, 1898.

4. Price, G. E.: Familial Lateral Sclerosis (Spastic Paralysis), J. Nerv. & Ment. Dis. **90**:51-55, 1939.

5. Bell, J., and Carmichael, E. A.: On Hereditary Ataxia and Spastic Paraplegia, Treasury of Human Inheritance, London, Cambridge University Press, 1939, Vol. 4, Pt. 3.

had a daughter (G. Ze.'s great-grandmother), who was also said to have had the disease. The great-grandmother had three daughters and two sons. In all these children there developed a progressive difficulty in the use of their lower extremities.

Of the third, and totally affected, generation, one male and one female had no children; one male had two affected sons; one female had one diseased daughter, and another female (G. Ze.'s grandmother) had two affected daughters and one normal son. G. Ze.'s grandmother died at the age of 78. The cause of her death was not known. She began to have difficulty in the use of her lower extremities when she was in her early 30's. In the last decade of her life she was paraplegic.

G. Ze.'s mother had died in her late 60's of an unknown cause. She first exhibited her difficulty in gait at about the age of 25. Her sister had died at the age of 78 but had not had trouble in walking until she was 70. Her disability was rapidly progressive, was limited to the lower limbs, and ended with complete paralysis of these extremities.

G. Ze.—*History.*—G. Ze., a white man, born in 1893, was first seen in 1941, at the age of 48. He gave a history of insidious onset of stiffness and weakness of the lower extremities at about the age of 34. The left lower extremity was involved first, and the right one about four years later. The condition had progressed very slowly. The patient was still able to work as a janitor. The only other symptoms were occasional difficulty in starting the urinary stream and frequency of urination.

Fig. 1.—Pedigree of family Ze., of seven generations. In six generations there were 19 afflicted members (8 females; 11 males).

In 1929 this patient was discovered to have a 4+ Wassermann reaction of the blood. However, at that time, when the condition involving his lower extremities was already present the spinal fluid was normal. He received a long, vigorous course of antisyphilitic therapy with arsenicals and heavy metals, including 120 injections of tryparsamide. Serologic reactions of the blood for syphilis became negative. There were never clinical indications of syphilis. The course of his neurologic condition was not influenced by the antisyphilitic therapy, for it continued to progress slowly, as it had done before.

Neurologic Examination.—He exhibited no disturbance in the mental sphere. The cranial nerves showed no changes. Coordination was normal in the upper extremities but was interfered with in the lower extremities by the presence of spasticity. The patient used a cane and walked with a "scissors gait." There was marked spasticity of the muscles of the lower extremities but only slight motor weakness. His feet were held in an equinovarus position. Muscle power, tone, and volume seemed normal elsewhere in the body. No fasciculations were noted. There were no abnormal involuntary movements. All modalities of sensation were intact throughout. The deep and superficial reflexes of the upper extremities were bilaterally hyperactive, but equal. The Hoffmann sign was present bilaterally. The abdominal reflexes were absent, but the cremasteric reflexes were present bilaterally. All the deep reflexes of the lower extremities were markedly, and equally, hyperactive. Ankle clonus and Babinski, Chaddock, and Rossolimo signs were present bilaterally.

Studies.—The Wassermann reaction of the blood was negative. The cytologic and chemical constituents of the spinal fluid were normal, and tests for syphilis gave negative reactions. The Queckenstedt test revealed no evidence of block of the spinal subarachnoid space. Roentgenograms of the thoracic and lumbar vertebrae showed no pathologic change. The results of complete blood cell counts and urinalyses were within normal limits.

F. Ze.—*History.*—F. Ze., a white man aged 47, born in 1895, was first seen in 1942. He gave a history of stiffness beginning in both lower limbs at about the age of 18. This condition progressed gradually, with increasing difficulty in walking, for about 20 years, after which the patient was confined to a wheel chair. The rest of the systemic review revealed no symptoms of any sort.

Neurologic Examination.—The patient was somewhat sluggish in his mental processes. The cranial nerves were normal except for slight anisocoria. The right pupil was somewhat smaller than the left, but both pupils reacted well to light and in accommodation-convergence. There was a marked intention tremor of both hands, more pronounced on the left side. There was a moderate degree of dyssynergia in the movements of the upper extremities. The patient was unable to walk or stand and showed pronounced spasticity of the muscles of both lower extremities. He was unable to move the legs, feet, or toes and showed pronounced weakness of the thighs. Muscle power was good in the upper extremities. There was no evidence of muscle wasting. There were no fasciculations or abnormal involuntary movements. All modalities of sensation were intact throughout. In the upper extremities the reflexes were bilaterally hyperactive, but equal. There was a bilateral Hoffmann sign. The deep reflexes in the lower extremities were extremely hyperactive, with Babinski and Chaddock signs. Ankle clonus was present bilaterally. Some induration and discoloration of the skin were noted in both legs and feet.

Studies.—Serologic tests of the blood for syphilis gave negative reactions. A complete blood cell count was normal.

M. Ze.—*History.*—M. Ze., a white man aged 52, born in 1890, brother of G. Ze. and F. Ze., was first seen in 1942. There was a history of stiffness and weakness of both lower extremities, beginning at the age of 8 years. The course was slowly progressive, with increasing difficulty in walking, so that the patient was unable to work after the age of 30. He had had urinary frequency, dysuria, and nocturia for approximately 40 years. There were no other symptoms.

Neurologic Examination.—When he was first seen, his mental status was normal. The cranial nerves were intact. Coordination of the upper extremities was normal. Equilibratory and nonequilibratory coordination in the lower extremities was interfered with because of muscular weakness and spasticity. The gait was of the "scissors" type, with marked spasticity. The patient was unable to walk without the use of two canes. There was generalized weakness of both lower extremities. Muscle power in the rest of the body was good and equal on the two sides. There was no wasting of muscles. No fasciculations or abnormal involuntary movements were observed. Sensation was intact in all modalities. The reflexes were slightly hyperactive in the upper extremities. The Hoffman sign was not elicited. The abdominal and cremasteric reflexes were present. There was marked hyperreflexia in the lower extremities, with bilateral Babinski and Chaddock signs and bilateral ankle clonus.

Studies.—The Wassermann reaction of the blood was negative. A complete blood cell count was within normal limits.

J. Ze.—*History.*—J. Ze., a white man aged 62, born in 1880, brother of G. Ze., M. Ze., and F. Ze., was first seen in 1942. Onset of illness was insidious, beginning approximately at the age of 45 with stiffness of both lower extremities. He was forced to give up driving a truck because he was unable to move his legs as quickly as formerly. However, he was able to continue working until the age of 52. He had to use one cane to walk after 1932. Then, from 1940 on, he had to use two canes. He had had slight difficulty in starting the urinary stream for a year and had begun to notice increased urinary frequency. His urinary difficulties necessitated a prostatectomy for benign hypertrophy in 1942. There were no other symptoms.

Neurologic Examination.—When first seen, the patient was mentally clear. The cranial nerves were intact. Coordination tests were well performed in the upper extremities. Both equilibratory and nonequilibratory coordination were somewhat disturbed in the lower extremities because of spasticity. His gait was "scissors" in type, with increased adduction of the thighs.

There was a marked increase in tone of the muscles of both lower extremities, together with weakness of these muscles, perhaps greater distally. There was no evidence of muscular weakness elsewhere in the body. There was no atrophy or fasciculation of muscles. Abnormal involuntary movements were not seen. Sensation was intact throughout in all modalities. The biceps, ulnar, and radial reflexes were slightly hyperactive on the left. The Hoffmann sign was not obtained. The abdominal and cremasteric reflexes were present. There was marked hyperreflexia in both lower extremities, with Babinski, Chaddock, and Rossolimo signs.

Studies.—The Wassermann reaction of the blood was negative. Tests of the spinal fluid showed an entirely normal state. A complete blood cell count was found to be within normal limits.

Family Ec. (Fig. 2).—This family was represented by my studies of a brother (W. Ec.) and a sister (S. We.). Their father was living and well in 1946, at the age of 75. Their mother had died at the age of 69, of an unknown cause. She had walked with a limp. This was presumed to have been due to "poliomyelitis," which she contracted at the age of 3. The process was not progressive.

The siblings of my patient (S. We.) had all been normal. They died at the ages of 17 years, 5 years, and 9 months. The causes of their deaths were not known.

Fig. 2.—Pedigree of family Ec. Only a brother and a sister had progressive spastic weakness of the lower extremities.

S. We.—*History.*—S. We., a white woman, was first examined in August, 1946, at the age of 53. Three years before, at the age of 50, she had noted a tendency to stumble with the left foot, accompanied by a tingling sensation in this foot and leg. The left lower extremity gradually became stiff, and then the right lower extremity became involved in a similar manner. There was a gradual increase of these symptoms, but there were no other disturbances.

Neurologic Examination.—The patient was of average intelligence with no evidence of a mental disturbance. The cranial nerves were intact, except for 25% of "conduction-type" hearing loss in the left ear. This disturbance had followed otitis media, which had developed after an acute infection of the upper respiratory tract two weeks before examination. The gait was spastic. The Romberg test gave a negative result. Nonequilibratory coordination tests were performed well in the upper extremities. There was moderate ataxia bilaterally in doing the heel-to-knee test. There was increased muscular tone in both lower extremities, being more pronounced on the left. There was slight weakness of the muscles of both lower extremities, being greater on the left and more pronounced distally. There was no atrophy or fasciculation of the muscles. There were no abnormal involuntary movements. Sensation was intact in all modalities. The deep and superficial reflexes were equal bilaterally and hyperactive in all four extremities. The Babinski sign and confirmatory signs were present bilaterally. Hoffmann's sign was present in both hands. The abdominal reflexes were absent.

Studies.—The Kolmer and Kline reactions of the blood were negative. A complete blood cell count and urinalysis gave normal values. Gastric analysis showed the presence of free hydrochloric

acid. Roentgenograms of the skull, chest, and entire spine showed nothing abnormal. Examination of the cerebrospinal fluid revealed 75 mg. of protein per 100 cc. and no cells; the colloidal gold curve was normal, and tests for syphilis gave negative reactions. There was no evidence of block of the spinal subarachnoid space with the Queckenstedt test.

Course of Illness.—The patient was reexamined two years later (1948). She still walked without support, but with more difficulty. She believed that her legs were more spastic than before. However, neurologic examination at this time showed little change from the previous status. No new signs had developed.

W. Ec.—*History.*—W. Ec., a white man, the brother of S. We., was first seen in 1941, at the age of 43. In 1933, when he was 35, he noticed unpleasant paresthesias in the left leg, chiefly in the sole. This persisted intermittently up to the time when he was last seen, in 1946. In 1938 he first noticed difficulty in the use of his left lower extremity, due to stiffness. This had increased without remissions. In 1940 he began having similar trouble with the right lower extremity. About this time he noticed poor handwriting and slight difficulty in the use of his hands. When he was first seen, he thought that the difficulty in the upper extremities had lessened to some extent. He had noticed slurring of speech at the time of the onset of his illness, but this may have been due to a poorly fitting dental prosthesis. There were no other symptoms.

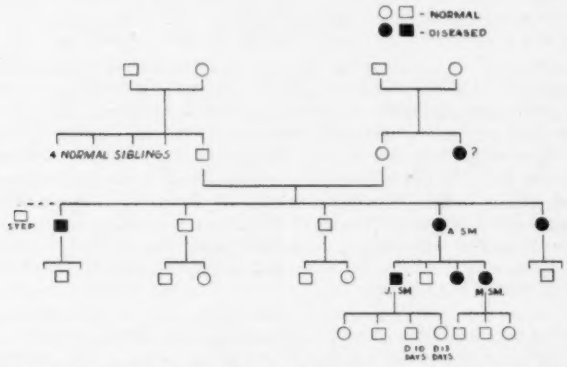

Fig. 3.—Pedigree of family Sm., of five generations. In three generations seven members (five females; two males) were afflicted.

Neurologic Examination.—In 1941 the patient was normal mentally. The slight slurring of his speech was noted then, but the cranial nerves seemed intact. Both equilibratory and non-equilibratory coordination were normal except for slight incoordination in the heel-to-knee test; this appeared to be due to the spasticity and weakness of his lower extremities. Gait was spastic, with marked increase in the tone of the muscles of both lower extremities. Greater weakness was noted in the muscles of the left leg and the flexor muscles of the left thigh. There was no atrophy or fasciculation of muscles. Abnormal involuntary movements were not noted. Sensation was entirely normal in all modalities. The deep and superficial reflexes were hyperactive in the upper extremities, being slightly more so on the left. Hoffmann's sign was present on the left. There was pronounced hyperreflexia in the lower extremities, with the presence of patellar and ankle clonus, a Babinski sign, and confirmatory signs bilaterally. The upper abdominal reflexes were absent.

Reexamination in 1946 showed essentially the same picture, but with evidence of progression. The patient was then able to walk only with considerable difficulty, and with the aid of two canes. Examination at this time showed essentially the same condition as before except that the lower abdominal reflexes were now absent. There was slight disturbance of posture holding and check movements in the upper extremities.

Studies.—In 1947 the Kolmer and Kline reactions of the blood were negative. Urinalysis and a complete blood cell count gave normal values. A roentgenogram of the entire spine revealed no abnormality. Examination of the spinal fluid showed nothing abnormal. There was no evidence of block of the spinal subarachnoid space with the Queckenstedt test.

Family Sm. (Fig. 3.).—The information concerning the first and second generations was obtained from A. Sm., of the third generation. She knew that her grandparents did not have any such disease and that her parents were well, but her mother's sister was supposed to have been "crippled in the legs," although no details of this woman's condition were available.

A. Sm. had had a stepbrother who had died in childhood, but he had never had any trouble with his lower extremities. One of her sisters had progressive paralysis of her lower extremities, so that by the time she died, at the age of 60, she was completely unable to walk. This woman began to have trouble at the age of 10. She may have had convulsions. Her one affected brother began to exhibit his difficulty in walking at the age of 60. Three of her four children had onset of the disease at the ages of 40, 31, and 25, respectively. Her one afflicted son had four children, none of whom had yet manifested the disease. Two of these children were in their 20's. A boy died at the age of 10 days, and a girl died of tuberculosis, at the age of 13.

A. Sm.—*History.*—A. Sm., a white woman, was first seen in 1946, at the age of 69. Trouble in walking began in the fifth decade of life with stiffness in both lower extremities. She thought that this difficulty had progressed slowly at first, but that there had been little change for about 10 years. The only other symptom was urinary incontinence, which had begun a year prior to examination.

Neurologic Examination.—The patient was mentally clear. She showed no abnormality of the cranial nerves. Tests of nonequilibratory coordination were well performed in the upper extremities. Tests for coordination of the lower extremities were interfered with by the presence of spasticity. The patient showed an extremely spastic gait. She was able to walk only with support. There seemed to be slight weakness of the muscles of the lower extremities, but no weakness elsewhere in the body. There was greatly increased tone in the muscles of both lower extremities. There was no evidence of muscular atrophy or fasciculations. Sensation was intact in all modalities throughout. The deep and superficial reflexes were bilaterally equal and active in the upper extremities. The Hoffmann sign was not elicited. The deep reflexes in the lower extremities were hyperactive except for the ankle jerk, which was poorly obtained bilaterally. There were bilateral Babinski and Chaddock signs.

Studies.—The Kolmer and Kline reactions of the blood were negative. A complete blood cell count was normal. A roentgenogram of the vertebral column showed rather extreme kyphosis, with compression of the bodies of the 10th and 11th thoracic vertebrae. These changes were interpreted as being due to mechanical change rather than to bone disease.

Course of Illness.—The patient died of pneumonia in October, 1947, 14 months after she was first seen. According to her daughter, her condition at that time was essentially the same. Unfortunately, permission for autopsy was not obtained.

M. Sm.—*History.*—M. Sm., the daughter of A. Sm., was first seen in 1946, at the age of 42. She gave a history of insidious onset of stiffness and weakness of both lower extremities. She believed her symptoms began at about the age of 30, after a rather severe attack of "influenza." The condition progressed very slowly. She thought there had been little progression in the past few years. There had been no remission. Subjectively, she noted painful pulling sensations in the calves of both legs. She thought that she was "nervous." With her menses there developed urinary frequency and an increased number of sharp pains in her legs. She had occasional blurring of vision.

Neurologic Examination.—The patient was mentally clear. She showed no abnormality of the cranial nerves. Performance in the coordination tests was good in the upper extremities but was somewhat impaired in the lower extremities, owing to the spasticity. The patient walked with an extremely spastic, "scissors" gait, but she was able to walk without support, although slowly. There was a moderate degree of generalized weakness of the lower extremities. The weakness and the increased tone were slightly more pronounced on the left side. There was no evidence of atrophy or fasciculation of muscles. There were no abnormal involuntary movements. The jaw reflex was hyperactive. The reflexes of the upper extremities were increased bilaterally. The

Hoffmann sign was elicited bilaterally. The abdominal reflexes were absent. The knee and ankle reflexes were hyperactive. There was transient ankle and patellar clonus. The Babinski and confirmatory signs were elicited bilaterally. Sensation was normal throughout in all modalities.

Mental Examination.—The patient showed nothing unusual in her attitude and general behavior. Her affect seemed appropriate. Her thought content disclosed a tendency toward loosely held paranoid ideation. This was not marked. Her sensorium was clear. She was of apparently average intelligence. Her speech itself was normal, but there was a disorder of phonation, consisting of frequent short periods of a forced, high-pitched, squeaking voice. This occurred with no apparent precipitating cause, lasted only one or two minutes, and returned to normal spontaneously. (No one else in the family was similarly affected.)

Studies.—The Kolmer and Kline reactions of the blood were negative. A complete blood cell count and urinalysis gave normal values. A gastric analysis showed a normal amount of free hydrochloric acid. Examinations of the spinal fluid for cells and protein gave normal values; the colloidal gold curve was normal, and tests for syphilis gave negative reactions. Roentgenograms of the vertebral column showed no abnormality. The Queckenstedt test revealed no block of the spinal subarachnoid space.

Course of Illness.—The patient was seen several times in the course of the next two years; her condition remained essentially the same. There was no definite evidence of progression, objectively or subjectively. Her dysarthria persisted off and on. Direct laryngoscopic examination revealed no local disease to account for this difficulty. The disturbance was thought by some to represent a conversion phenomenon.

J. Sm.—*History.*—J. Sm., the son of A. Sm. and the brother of M. Sm., was first seen in 1947, at the age of 45. He had first noticed stiffness and pain in both lower extremities in 1941, at the age of 39. There had been slow progression, so that on admission he had some difficulty in walking, owing to the spasticity. He could no longer run. There had been no remission.

Neurologic Examination.—The patient was mentally clear. The cranial nerves seemed to be intact. Coordination was normal in the upper extremities. Performance in equilibratory and nonequilibratory coordination tests was interfered with by the spasticity of the lower extremities. He walked with a spastic gait, dragging the toes of his right foot. There was slight weakness of the muscles of both lower extremities, being more pronounced on the right side. Muscle tone was increased in both lower extremities. There was no atrophy or fasciculation of muscles. There were no abnormal involuntary movements. The triceps, radial, and ulnar reflexes were hyperactive on the left. All the deep reflexes of the lower extremities were hyperactive and equal. The abdominal and cremasteric reflexes were absent. There were Babinski and confirmatory signs bilaterally. Sensation was normal throughout in all modalities.

Studies.—The Kolmer and Kline reactions of the blood were negative. A complete blood cell count and urinalysis gave normal values. Roentgenograms of the vertebral column disclosed nothing abnormal.

Course of Illness.—Since he was first seen, the patient's disease had shown little progression, except possibly a slight increase in the spasticity of the muscles of his lower extremities. He had no other symptoms except for occasional feelings of tightness in the leg muscles. He had been able to continue his work as a janitor.

Family Ha. (Fig. 4).—The maternal grandfather of my first patient, K. Ha., was living in 1950, at the age of 88, although he was blind. All his (K. Ha.'s) mother's siblings were deceased, but there had been no difficulties "in that side of the family."

His father's siblings were all dead. His father had been a "heavy drinker" and had died at the age of 69, of an unknown cause. He was said to have had some difficulty in walking and to have had spasms and weakness of his lower limbs during the last few years of his life. K. Ha.'s mother was well, at the age of 70.

The first patient's father had had four children in a first marriage. One of these children died in infancy; the other died at the age of 46, his death supposedly being related to his having been "gassed" in World War I. (The first wife died of tuberculosis.)

The first patient was the sixth born of eight children. He was married and had a healthy son, aged 5 years. The youngest brother was known to have some sort of "leg trouble." The

oldest sister (G. Ke.) had had her "walking trouble" since her early teens. This sister's youngest daughter was beginning to have difficulty in the use of her lower extremities, but the other children seemed well.

K. Ha.—*History.*—The patient was seen in 1950, at the age of 40. The onset of his difficulty in walking was at the age of 10. It began gradually as inability to put the heel of his right foot on the ground, so that he had to walk on the ball of his right foot. The difficulty with his right lower extremity slowly progressed. Low-back pain developed at the age of 30. At about the age of 32 he began to have trouble in using his left lower extremity. The difficulty in walking had become progressively worse, so that the patient had had to use canes for at least six years.

Neurologic Examination.—The patient was mentally clear. The cranial nerves seemed to be intact. The patient could walk only with support; even then his lower extremities were held in a partially flexed position. His gait was markedly spastic and of the "scissors" type. Coordination tests were well performed in the upper extremities, and the degree of coordination could not be determined in the lower extremities because of the increased tone of the muscles. This tone was even more pronounced when the patient was upright. There was no change in muscle power, tone, or volume in the upper extremities. There was no wasting of muscles of the lower extremities, but perhaps slight contracture of the flexors of the legs and thighs had already developed. There were no fasciculations. There were no abnormal involuntary movements. The

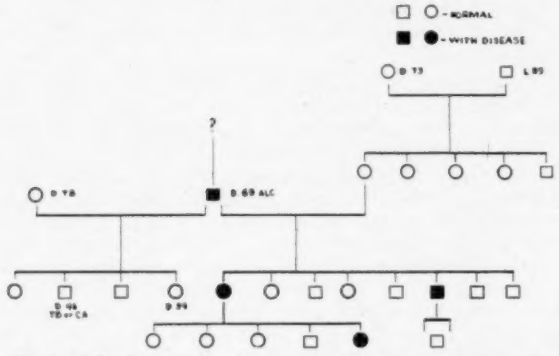

Fig. 4.—Pedigree of family Ha. In three generations there were four diseased members (two females; two males).

sensory system was intact in all modalities. The deep reflexes were hyperactive in all the extremities. There was patellar and ankle clonus bilaterally. The abdominal reflexes were present. The Hoffmann, Babinski, Chaddock, and Rossolimo signs were obtained bilaterally.

Studies.—The Kolmer and Kline tests of the blood were negative. The results of a complete blood cell count and urinalysis were within normal limits. Free hydrochloric acid was found in the gastric juice. The spinal fluid was under normal pressure. It contained 48 mg. of protein per 100 cc. The Kolmer reaction of the cerebrospinal fluid was negative, and the mastic test was normal. The Queckenstedt test showed no block of the spinal subarachnoid space. The roentgenograms of the chest, skull, and vertebrae revealed no abnormalities.

G. Ke.—*History.*—G. Ke., a woman born in 1899, was examined in 1950, when she was 51. At the age of 11 or 12 years she began to have difficulty in going up and down stairs. By the age of 14 she began to have trouble in walking on level ground, and by the age of 20 she was having painful spasms in her leg muscles and was walking more and more on her toes. Her legs and feet were put into plaster casts for four months when she was 27. Since then, the disturbance in the use of her lower extremities had been slowly progressive, and she thought that it had been much worse in the five years prior to examination.

She had had no bowel or bladder difficulties. For four or five years she had complained of vague paresthesias in her left hand and leg.

She was married in 1920 and had had one miscarriage. Her husband was living and in good health.

Neurologic Examination.—The patient was mentally clear. No abnormalities were noted in the cranial nerves. She was barely able to get about with the aid of two canes. She had a markedly spastic "scissors" gait. The Romberg sign was not elicited. Nonequilibratory coordination tests were well performed in the upper extremities, but could not be studied in the lower extremities because of the spasticity and weakness. Muscle tone and power were normal in the upper extremities. Muscle tone was greatly increased in the lower extremities, and muscle power was diminished. There were no fasciculations or evidences of muscle wasting. The muscles of the lower extremities seemed to show early contractures. The sensory system was intact in all modalities. The jaw reflex was active. The deep and superficial reflexes of the upper extremities were hyperactive, but equal on the two sides. The Hoffmann sign was elicited on both sides. The abdominal reflexes were absent. The patellar and hamstring reflexes were obtained with difficulty, and the ankle jerk was absent. (These changes were thought to be due to spasticity and contracture.) The Babinski reflex and confirmatory signs were obtained bilaterally.

J. Ke.—*History.*—J. Ke., a girl aged 16, was examined in 1950, when she was in her ninth month of pregnancy. For about three years she had noticed occasional difficulty in walking, running, and going up or down stairs. This was especially noticeable when she was excited or under tension. When she had been a cheer leader in high school, she had had difficulty because the excitement made her "legs stiff." For several years she had had painful spasms of her leg muscles. Her symptoms were more pronounced in the right lower extremity. A year before examination she had had spontaneous clonus of her right foot, which she was able to stop by pushing her foot down hard on the floor. There were no bowel or bladder symptoms. She had noted no subjective sensory disturbances.

Neurologic Examination.—The neurologic examination at this time revealed a Babinski sign on the right and an equivocal Babinski sign on the left. Otherwise nothing abnormal was noted.

PATHOLOGIC STUDY OF A CASE (FIG. 5)

Family Fo was first described by Bayley[6] in 1897. Then, in 1902, Spiller[7] again gave the history of this family and described in detail two cases, those of C. Fo. and his son, F. B. Fo. I am concerned with the case of C. Fo.

C. Fo., a white man, a member of the fourth generation of his family to be so affected, was seen by Spiller in 1902, at the age of 32. The history and findings on examination at that time were given as follows:

The onset of the disease was at the age of 5 years with hyperadduction of both thighs. Gradually there followed general spasticity and weakness of both lower extremities. Examination at that time showed a spastic gait, with bilateral equinovarus. There was weakness of the legs, with very little voluntary movement of the feet and toes. The weakness and spasticity were more pronounced on the left. The deep reflexes were exaggerated. There were ankle clonus and a Babinski sign bilaterally. There was no atrophy or fasciculation in the affected musculature. Sensation was normal, and there was no change in the electrical reactions. The upper extremities were noted to be normal. The findings at that time indicated little or no progression of the disease in the five years following the initial description by Bayley.[6]

C. Fo. had three sons. One of them, H. B. Fo., was also studied by Spiller and noted to have a spastic paraparesis resembling his father's condition. The onset was noted when the child began to walk, at the age of 18 months. Another son, aged 3 years at the time, was reported by the mother to have "weak knees"; but examination then revealed no abnormality. However, when another branch of the family was reported on in 1933 by Rechtman and Alpers,[8] it was noted that spastic paraparesis had later developed in this child.

6. Bayley, W. D.: Hereditary Spastic Paraplegia, J. Nerv. & Ment. Dis. **24**:697-701, 1897.

7. Spiller, W. G.: Fourteen Cases of Spastic Spinal Paralysis Occurring in One Family, Philadelphia M. J. **9**:1129-1131, 1902.

8. Rechtman, A. M., and Alpers, B. J.: Hereditary Spastic Paraplegia: Occurrence of the Condition in Five Generations with Presentation of Two Cases, Arch. Neurol. & Psychiat. **32**:248, 1934.

A third son was reported as being normal in 1902 and was not recorded as affected at the age of 66, in the report by Alpers and Rechtman in 1933.

C. Fo. died in 1936 of carcinoma of the gall-bladder with generalized peritoneal metastases. On hospital admission at this time the fact that he had spastic paraplegia was noted, but no history or examination relevant to his neurologic status was recorded. However, the statement was made that, aside from the paraplegia with swelling of the feet, which had been present since childhood, and the recent symptoms of abdominal distention and dyspnea, no symptoms or abnormalities were noted. A complete autopsy was done.

The brain was so poorly preserved that adequate study of it was not possible. Sections were made of the spinal cord, medulla, and pons and prepared by the Pal-Weigert method.

Spinal Cord.—Lumbar Region (Fig. 6): Bilateral incomplete demyelination of the lateral corticospinal tract, the rubrospinal tract, and possibly the dorsal spinocerebellar tract, was noted. The demyelination was located peripherally, was most marked in the lateral columns, and was more evident on one side than on the other. Slight involvement of the ventral funiculus was also noted.

Lower Cervical Region (Fig. 7): Pronounced demyelination was noted in this section. The fasciculi gracili showed slight diffuse thinning. The lateral and ventral columns were much more

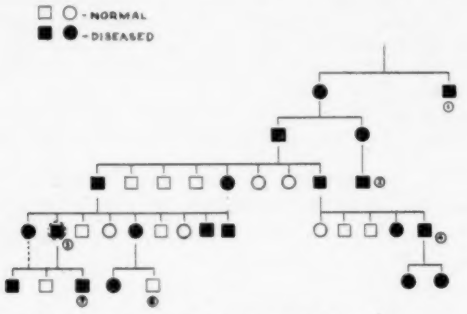

Fig. 5.—Pedigree of family Fo. (after Bayley [6] and Spiller,[7] as later modified by Rechtman and Alpers [5]).

(*1*) Sibling of original (?) afflicted female. This man is reported to have been similarly afflicted and to have had diseased descendants. (*2*) Branch reportedly with several members who had difficulty in walking. (*3*) C. Fo. patient whose case, including the autopsy, is reported in this paper. (*4*) cases reported by Rechtman and Alpers.[5] (*5*) Patient examined as a child by Spiller in 1902 [7] and found to be normal at that time, although his mother complained that he had "weak knees." As an adult he exhibited the typical familial picture. (*6*) Sibling who died in infancy, while normal.

The dotted line indicates that these members were known to be without issue.

affected. Again, one side seemed to be involved more than the other. Most of the changes were at the periphery of the cord. The greatest devastation seemed to be in the ventral funiculi. The lateral corticospinal tracts showed pronounced changes. The dorsal and ventral spinocerebellar tracts seemed also to be involved a bit. The ventral corticospinal tracts were somewhat demyelinated, as were the tectospinal tracts. The major damage involved the medial vestibulospinal tracts and a portion of the lateral vestibulospinal pathways.

The anterior horn cells of the spinal cord seemed to be intact.

Medulla, Caudal Limit of Fourth Ventricle (Fig. 8).—While the pyramids showed some thinning in the Pal-Weigert stain, it was not a marked process. Less fibers seemed to be present in the ventromedial portion of the pyramid. It was not possible to identify changes in other tracts noted to be involved in the cervical region of the spinal cord.

Pons, Level of Entrance of Superior Cerebellar Peduncle into Tegmentum (Fig. 9).—No definite changes could be noted in the fibers at this level.

Fig. 6 (C. Fo.).—Lumbar region of the spinal cord. Pal-Weigert stain; × 17.

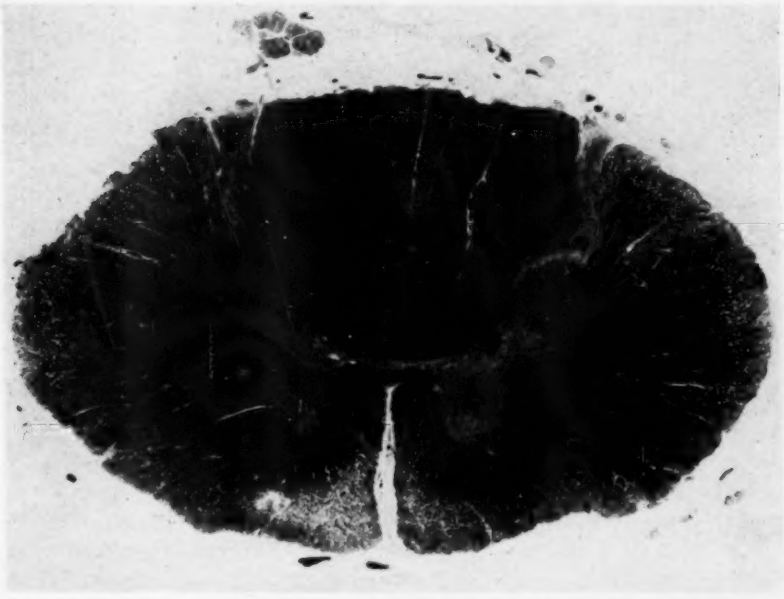

Fig. 7 (C. Fo.).—Lower cervical region of the spinal cord. Pal-Weigert stain; × 13½.

Fig. 8 (C. Fo.).—Medulla oblongata at level of interior olivary nuclei. Pal-Weigert stain; × 7.5.

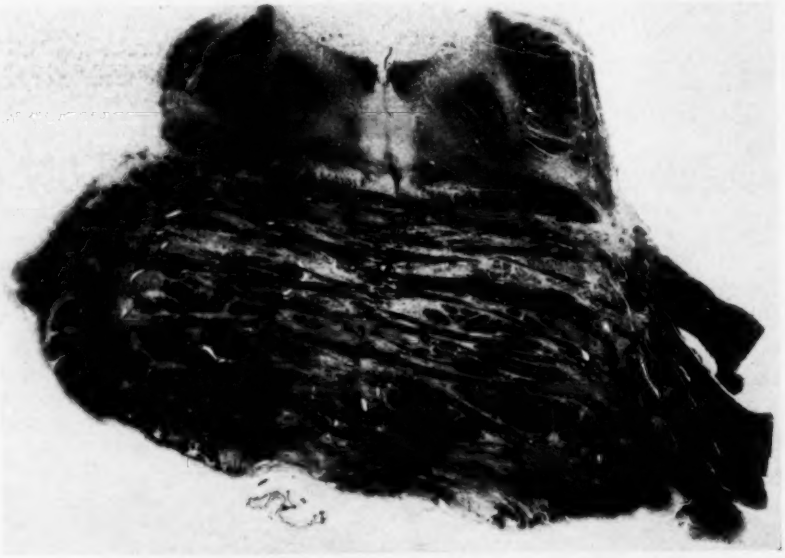

Fig. 9(C. Fo.).—Pons Varolii at level of entrance of superior peduncles into tegmentum. Pal-Weigert stain; × 4.4.

COMMENT

Clinical Summary of Present Cases.—I have studied 12 patients of 4 families, in which 32 members appeared to be afflicted by this disease. The data are summarized as follows:

Family	No. of Afflicted Persons Examined	Total No. of Afflicted Persons		
		No.	Females	Males
Ze.	4	19	8	11
Ec.	2	2	1	1
Sm.	3	7	5	2
Ha.	3	4	2	2
Total	12	32	16	16

The ages of onset of the disease as noted by the patients were extremely variable, even in a given family. The ages of onset were as follows:

Family	Ages at Onset of Symptoms, Yr.
Ze.	
Affected males	34, 18, 8, 45
Grandmother of G. Ze	Early 30's
Mother of G. Ze	25
Maternal aunt of G. Ze	70
Ec.	
Affected female	50
Brother of affected female	40
Sm.	
Affected brother of A. Sm	60
Sister	10
Three other siblings	40, 31, 35
A. Sm.	In 50's
Daughter of A. Sm	30
Son of J. Sm	39
Ha.	
One male	60
Son of affected male	10
Daughter of affected male	11 or 12
Young girl with developing disease	13

Occasionally, there were preceding or associated subjective sensory symptoms. These were invariably evanescent. While one side may be affected sooner than the other, in most of my cases the disease had begun bilaterally. Its onset was insidious, and the disease had progressed slowly and unremittingly over many years. It was essentially with progressive weakness and stiffness of both lower extremities, leading finally to paralysis. Only one patient noted any weakness or impaired use of the upper extremities.

In no case were the cranial nerves involved; the sensory system was intact in all modalities; the mentality was normal; spastic paraparesis or paraplegia with hyperreflexia was present. In only a few instances was incoordination noted, and it was slight. The reflexes in the upper extremities were invariably abnormal, despite absence of subjective motor difficulties in these extremities. No sphincter disorders were noted.

In all cases there was a family or sibling history of the condition.

In none of the cases I could study was there any laboratory evidence of diabetes, syphilis, pernicious anemia, spinal-cord tumor, vertebral disease, or any other condition known to produce the syndrome of lateral sclerosis.

It is this constellation of symptoms and signs which I believe allows one to designate these cases as instances of the "pure" hereditary form of spastic paraplegia. Such cases are clinically vastly different from the many cases with similar diagnosis reported in the literature in which the motor symptoms are really but one of numerous indications of disease of the nervous system.

Clinical Reports in Literature.—Rhein,[9] in 1916, found 111 families with this condition in his review of the literature and described 4 cases of spastic paraplegia in one generation. Then, in 1933, Paskind and Stone[10] described the neurologic findings in three idiotic brothers with spastic paraplegia. They collected the cases in the literature from Rhein's report up to their own and found the number of recorded families to be 152. Price,[4] in 1939, reported on a family with this condition in which the disease occurred in seven females over four generations. He examined three females, of whom two (a woman of 30 and a 2-year-old daughter) had spastic paraplegia and one (a girl of 7 years) had ataxic paraplegia. He found five additional families reported since Paskind and Stone's report, bringing the total to 158 families.

In 1939, also, Bell, assisted by Carmichael,[5] collected from the literature 273 pedigrees of Friedreich's ataxia, ataxic paraplegia, and spastic paraplegia and added 46 new pedigrees. She excluded pedigrees which reported only single cases as providing "no evidence of genetic potentiality." In her attention to spastic paraplegia, she studied 74 pedigrees, with a total of 316 diseased members, and added one pedigree of her own.

Not all the literature up to 1950 has been available to me. However, in the following summary most of the studies reported in the literature since 1939 are noted.

King[11] examined a man of 45 whose disease began at the age of 29 with weakness and stiffness of the right lower extremity. At the age of 36 the left lower extremity became involved. The patient presented slowly progressive spastic paraparesis. He had a brother who began to manifest the disease at the age of 40, two sisters in whom the disease had its onset at the ages of 28 and 41, respectively, and a 17-year-old-nephew in whom the condition was beginning to develop. His mother and grandmother had had the disease, the former having onset of symptoms at the age of 38.

Gonzalez Enriquez and Valenzuela[12] described a family of five children—four boys and one girl. In three brothers, aged 12, 11, and 9 years, progressive weakness of the lower extremities had developed. The oldest boy's disease progressed rapidly from the age of 8 years. He had flaccid paraplegia with hyperreflexia, and the Babinski sign was present bilaterally. The 11-year-old boy began to have his disability in gait at the age of 7 years. This, too, progressed rapidly, and the child had not walked for a year and a half. He had paraplegia, flaccid in the leg muscles and spastic in the thighs, but with increased and abnormal reflexes. The 9-year-old

9. Rhein, J. H. W.: Family Spastic Paralysis, J. Nerv. & Ment. Dis. **44**:115-144, 224-242, 1916.

10. Paskind, H. A., and Stone, T. T.: Familial Spastic Paralysis: Report of Three Cases in One Family and Observation at Necropsy, Arch. Neurol. & Psychiat. **30**:481-500, 1933.

11. King, H. N.: Familial Spastic Paralysis, Veterans Admin. Tech. Bull. **18**:332-333, 1942.

12. Gonzalez Enriquez, R., and Valenzuela, R. H.: Paraplejía espasmódica familiar progresiva, Rev. mex. pediat. **13**:212-228, 1943.

boy began to have trouble at the age of 8 years. He had had paraparesis, with more involvement on the right. A maternal aunt was presumed to have a similar disturbance.

Crowe [13] reported on five children in one family (four girls and one boy). All had spastic weakness or paralysis of their lower extremities. Their parents were healthy, and no other members of their families were known to have the disease. Three of the children had clubfeet, and four of them had some form of strabismus.

Cienfuegos and Daneri [14] described a family in which there were three boys and three girls. All the girls were well. A boy of 8 years had difficulty in walking, apparently from birth, with scanning speech and mental retardation at an imbecile level. He had paraplegia in flexion. His 13-year-old brother had started to walk on his toes and then had progressive difficulty in walking, so that he soon needed canes. He, too, had scanning speech and spastic paraparesis with hyperreflexia. A 15-year-old brother also had had trouble in walking from the beginning. This disability was progressive spastic paraparesis, and when examined he had weakness of his upper extremities, scanning speech, paraplegia in flexion, and mental retardation. All these afflicted boys were said to have "secondary optic atrophy." In all, the difficulty in the use of the lower extremities was progressive.

Kastan [15] described four members of one family—a man, his two male children, and their paternal male cousin. On clinical grounds, he thought that the 34-year-old father had Pelizaeus-Merzbacher disease (aplasia axialis extracorticalis congenita), that the 25-year-old male cousin (although never examined) had spastic spinal paralysis, and that the two sons, who had died at the ages of 4 and 7 years of a progressive neurologic disorder with pleocytosis of the cerebrospinal fluid, were suffering from leucodystrophy. Despite these differences in the clinical pictures, they all had one sign in common, viz., spastic paraparesis. He concluded, "Therefore, it is suggested that familial spastic paralysis be classified as the spinal type of diffuse sclerosis."

Jéquier, Michail, and Streiff [16] described 14 cases in two generations of one family. Nine members showed neurologic signs—spastic paraplegia, which began early in life and was slowly progressive; sensory changes of "neuritic" type, mostly in the lower limbs and involving deep sensation more than superficial sensation, and some trophic and circulatory changes in the lower extremities. In 5 members of another branch of the family, they found the juvenile form of macular degeneration. They noted that such macular changes have been reported hitherto only in cases of Friedreich's disease (hereditary sclerosis, spinal form) or Marie's heredocerebellar ataxia.

Louis-Bar and Pirot [17] described the cases of two brothers who showed spastic paraplegia and macular degeneration. In one of the brothers they noted an "amy-

13. Crowe, M. P.: Family Spastic Paresis with Strabismus, Arch. Dis. Childhood **19**:32-33, 1944.

14. Cienfuegos, E., and Daneri, J.: Paraplejía espasmódica familiar, Arch. argent. pediat. **22**:289-299, 1944.

15. Kastan, M.: Different Forms of Diffuse Sclerotic Process—Pelizaeus-Merzbacher Disease, Strümpell's Familial Spastic Spinal Paralysis, Leucodystrophy—in One Family, J. Nerv. & Ment. Dis. **101**:357-362, 1945.

16. Jéquier, M.; Michail, J., and Streiff, E. B.: Paraplégie familiale et dégénéresence tapétorétinienne, Confinia neurol. **6**:277-280, 1945.

17. Louis-Bar, D., and Pirot, G.: Sur une paraplégie spasmodique avec dégénéresence maculaire chez deux frères, Ophthalmologica **109**:32-43, 1945.

otrophy of the spinal type." They believed that another member of the family had an incomplete form of spastic paraplegia. Syndactyly was noted in three brothers and in a collateral relative. Other malformations were noted in this family.

Ulla [18] described the cases of a brother and sister who had spastic paraparesis. Both began to have their trouble at the age of 12 years. Both had spastic gait with increased and pathologic reflexes in the lower extremities, but without ataxia or sensory changes. They had six brothers, who had no such difficulty.

Planson [19] described a family of seven generations in which there were 17 afflicted members. He examined three healthy children of a paraplegic man of the sixth generation. In one of these children (a boy of 4 years) he found "the asynergy of Babinski," which he concluded was an early sign of cerebellar disease. He thought of these children as becoming the "future spastic or ataxic members."

Roger and Caïn [20] reported three families. In their first family, seven persons were involved in three generations. The mother in the first generation had trouble in walking and also had a speech disturbance. She had nine children; two of these died very young; of the seven living children, only one was symptom-free. Her four daughters had spastic paraparesis and some cerebellar signs in the upper extremities; her two sons had no signs of change in the lower extremities, but both had "intermittent enuresis." In the third generation, three children were apparently healthy, although one was said to be enuretic. In their second family, a brother and sister both had onset of progressive spastic paraplegia at the age of 6 years. The brother had some "cerebellar signs" in the upper extremities as well. The sister had beginning weakness of the upper extremities and dysarthria at the age of 12; then generalized convulsions developed, and she died, at the age of 15. Their third family showed the disease in three generations. A man, examined at the ages of 43 and 50, was found to have spastic paraparesis, which began at the age of 10 years. His paternal grandfather and aunt and his father had a similar difficulty.

Klingler and Bloch [21] described a progressive spastic paraparesis in eight generations of one family. Their first patient, a member of the sixth generation, had onset of his disease at the age of 45. Of his nine children, two boys and one girl showed spastic paraparesis; one boy and one girl had "pyramidal signs." Four of his 16 grandchildren were found to have "pyramidal signs."

Farago [22] reported on a family of four generations, three generations of which were involved. Eight members showed spastic paraparesis or paraplegia; four had signs suggesting similar early involvement. He described particularly a man in whom spastic paralysis of his lower extremities developed at the age of 40. This patient had impaired perception of pain below the umbilicus and disturbances of bowel and bladder control. He described in detail the pathologic findings of the nervous system of this patient.

18. Ulla, J.: Un caso de presentaçion familiar de paralisis espinal espasmodica, Medicina, Madrid **13**:435-438, 1945.

19. Planson: Paraplégie spasmodique familiale, Paris méd. **1**:105-108, 1946.

20. Roger, H., and Caïn, J.: Les paraplégies spasmodiques familiales du type Strümpell-Lorrain, Semaine hôp. Paris **22**:693-698, 1946.

21. Klingler, M., and Bloch, W.: Über eine Sippe mit spastischer Heredodegeneration, Schweiz. Arch. Neurol. u. Psychiat. **58**:273-285, 1947.

22. Farago, I.: Beitrag zur Vererbung und Pathohistologie der spastischen Spinalparalyse, Monatsschr. Psychiat. u. Neurol. **114**:161-178, 1947.

Preioni, Sneider, Benzecry [23] described spastic paraplegia in a brother (aged 26, an imbecile) and a sister (aged 18). The parents were healthy, and the patient's two other brothers were well. The girl had onset of her trouble in infancy, while her brother began to have his first weakness at the age of 16.

Correra [24] described in detail the neurologic findings in a woman aged 29. Her illness began with a disturbance of skilled movements of her hands and blurred vision. Then there developed a mild speech disturbance and difficulty in walking. Five years later she showed many signs of involvement of the nervous system other than the spastic paraparesis. Her grandmother was said to have had a spastic gait. She had three brothers who were well, two brothers who had a disturbed gait, and one sister who had an unsteady gait with increased reflexes of the lower extremities.

Bickerstaff [25] described a family in detail in which spastic paraplegia was found to have occurred throughout three generations (76 members). There were 18 affected persons. When he checked the supposedly uninvolved members of this family, he found seven who showed signs suggesting an incipient form of the disease. One other member, who had died, was thought to have had the fully developed syndrome; two others may have had an early form. "The severity of the disease appeared to have diminished in successive generations." Two children and two adults were noted to have involvement of the optic nerves; some members had clinical findings suggestive of cerebral diplegia, and one had changes reminiscent of amyotrophic lateral sclerosis.

Therefore, at least 17 pedigrees have been reported in the literature since 1939 in which spastic weakness or spastic paralysis of the lower extremities was noted to occur in a number of members of a family. In perhaps five of these families the spastic paraparesis or paraplegia was the only symptom ("pure form"),[26] and possibly four other families might be considered to belong in this group.[27]

Pathologic Reports in Literature.—Various authors have reported postmortem studies of the nervous system in cases of disorders diagnosed as familial spastic paralysis, hereditary spastic spinal paralysis, familial spastic paraplegia, familial multiple sclerosis, etc. These cases were first collected by Dobrochtow [28] and then carried into the papers of Rhein [9] and Paskind and Stone.[10] I have reviewed the original papers and have added additional reports.[29] It was felt that for further exposition

23. Preioni, C.; Sneider, D., and Benzecry, I.: Enfermedad de Strümpell-Lorrain (paraplejía familiar espasmódica), Prensa méd. argent. **34**:1318-1323, 1947.

24. Correra, M.: Paraplegia spastica familiare o sclerosi a placche familiare? Cervello **24**:321-344, 1948.

25. Bickerstaff, E. R.: Hereditary Spastic Paraplegia, J. Neurol., Neurosurg. & Psychiat. **13**:134-145,1950.

26. King.[11] Gonzalez Enrique and Valenzuela.[12] Ulla.[18] Third family reported by Roger and Caïn.[20] Klingler and Bloch.[21]

27. Crowe.[13] Planson.[19] Preioni, Sneider, and Benzecry.[23] Bickerstaff.[25]

28. Dobrochtow, M.: Ein Fall von hereditärer Familienerkrankung vom Übergangstypus zwischen spastischer Spinalparalyse und Friedreichscher Krankheit, Deutsche Ztschr. Nervenh. **49**:1-35, 1913.

29. (*a*) Strümpell, A.: Über eine bestimmte Form der primären combinirten Systemerkrankung des Rückenmarks, im Anschluss an einen Fall von spastischer Spinalparalyse mit vorherrschender Degeneration der Pyramidenbahnen und geringerer Betheiligung der Kleinhirn-

(*Footnote continued on next page*)

the clinical and pathological data should be available in more condensed form. The accompanying table has been created for this purpose.

As can be seen from a brief study of these cases, there is no uniformity in the pathologic findings. On the other hand, when one reviews the histories and neurologic findings, it becomes evident that these cases represent indeed a heterogeneous collection of disturbances of the nervous system. Actually, they have in common only the heredofamilial occurrence and the presence of weakness or paralysis of the lower extremities. The latter finding has been the pivotal point on which the authors have made their clinical diagnosis, while they have ignored many other symptoms and signs which might just as well have deserved nosologic designation.

There are 24 cases in this Table. Only seven of them—Strümpell's two cases,[29a,j] Newmark's 3 cases,[30] and the single cases of Jakob [29o] and of Kahlstorf [29u] and possibly four others—two of Bischoff's,[29g] the case of Raymond and Rose's,[29p] and the case reported by Farago [22]—seem to me to resemble each other clinically and to deserve to be included under the diagnosis "hereditary (familial) spastic paraplegia." The others constitute a hodgepodge of varied disorders of the nervous system, with the paraparesis or paraplegia simply one of the occurrences in the illness, not the main or only factor.

In the seven cases in which the clinical picture was more constant and uniform, there seems to be a fair uniformity of the pathologic findings. In three cases Betz

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30. Newmark, footnotes 29 h, i, l, and q.

cells were atrophic or were judged to be diminished in number. In only one case was any change noted in the internal capsule, cerebral peduncles, pons, or medulla. The lateral corticospinal tracts were involved symmetrically in all seven cases, chiefly at thoracic levels and less at upper cervical levels. The uncrossed pyramidal tracts were involved in only four cases, but always to a slighter degree. The spinocerebellar tracts were involved in four cases. The fasciculus gracilis was symmetrically demyelinated in all seven cases, and this was always more marked in the cervical levels. The cells of Clarke's column were diminished in two cases, and the anterior horn cells, in one, while the cerebellum, the basal ganglia, and the rubrospinal tract were changed in one case. The major changes, therefore, were noted in the spinal cord, particularly in the lower cervical and upper thoracic portions of this structure. Above the cervicothoracic level, the columns of Goll were most degenerated and below the cervicothoracic level the lateral corticospinal tracts were most involved. This suggests the possibility of some major process acting in this general locus, producing nucleodistal and corticodistal degeneration. In only a few cases were changes noted in the Betz cells of the precentral gyri; yet no changes have been traced through the internal capsule, cerebral peduncles, pons, and medulla. Are the changes in the Betz cells due to the distal axonal damage?

Of considerable interest is the persistent demyelination in the columns of Goll. This is difficult to correlate clinically, for apparently no one has found changes in posterior-column functions in their cases. Newmark [29q] never found them disturbed in his cases.

The unusual case of Raymond and Rose [29p] was not included in this analysis because of the apparent fluctuation in symptoms and signs throughout the life of the young woman. Even the authors wondered whether she had suffered from hysteria. Lassek,[31] however, recorded weakness or paralysis without indication of change in the pyramidal tracts at necropsy. The explanation of this has not been forthcoming.

General Considerations.—For many years, Gowers' concept of abiotrophy has been the chief explanation offered for the causation of the heredodegenerative diseases of the nervous system. This concept implies a kind of variable survival quality of neural cytoplasm, which may be inherited. This theory ignores other elements which must maintain the integrity of the neurone and its processes. Perhaps all these factors are not yet known. However, it might be that a failure in adequate development or function of these accessory structures is the basic difficulty, and not some strange survival quality of the neural cytoplasm itself. For instance, the long processes must be nourished in their course through the brain, brain stem, or spinal cord. The vascular supply of the nervous system is a somewhat variable formation. No adequate vascular studies of this system have been made in hereditary spastic paraplegia or, indeed, in any of the heredodegenerative diseases of the nervous system. Furthermore, some authors believe that the integrity of the myelin, and hence of the axis-cylinder, is somehow related to the interfascicular oligodendroglia. Possibly this element might be studied profitably in cases of this disease. Such studies might well add many complications to the problem; yet it seems that one must move away from the restricted idea of neural-tissue abiotrophy if the heredodegenerative diseases are to be better understood.

31. Lassek, A. M.: The Pyramidal Tract: Basic Consideratons of Corticospinal Neurons, A. Res. Nerv. & Ment. Dis., Proc. (1947) **27**:106-128, 1948; The Human Pyramidal Tract: An Analysis of Its Pathophysiological Status, Brain **73**:95-102, 1950.

Name of Author	Year of Publication	No. of Cases and Sex	Age of Onset	Age at Death, Yr.	Duration of Illness, Yr.	Clinical History	Genetic Factors
Strümpell [20a]	1886	1 M	38 yr.(?)	63	25	Gradually progressive weakness and stiffness of lower extremities; epileptic seizures	Family "Gaum"
Eichhorst [20b]	1896	2 F	36 yr.	42	6	Onset with slight fatigue and weakness of lower extremities; weakness progressed; then speech disturbed; vision next impaired; finally mental disorder	Mother and son
		M	8 yr.	9	1	Onset with weakness of lower extremities, which progressed; father thought he had never been completely normal; tremulousness of voluntary movements from birth; some visual difficulty Preferred to be alone, was morose and stubborn	.....
Pesker [20c]	1900	1 M	Birth (?)	24	24(?)	First convulsions at age of 15 days, continued almost daily until age of 2 Began to talk at age of 2, but never talked properly; never walked	Two paternal uncles had seizures, followed by paralysis; brother of patient had an almost identical disorder
Peskin [20d]	1900	1 M	6 yr.	16	10	Progressive weakness of lower extremities, so that by age of 14½ yr. he was confined to bed; difficulty in vision began at age of 6, and he was blind by age of 14; speech affected by age of 9; progressive impairment of intelligence to dementia; first convulsion at age of 6	One brother similarly afflicted
Bäumlin [20e]	1901	1 F	3¾ yr.	4¼	½	Patient began to squint occasionally; then at age of 4 yr. had infection of gastrointestinal system, followed by unsteady gait and frequent falling; a month later, movements of eyes and tremors of extremities noted by mother, who thought child's intelligence was impaired; patient became irascible and sulky; died in status epilepticus	Four sisters involved in this family, with onset and course almost identical in all
Bourneville and Crouzon [20f]	1901	1 M	18 mo.	16	14½	At 18 mo.: Measles Patient never walked afterward; spoke a little before, but not afterward At 2 yr.: Convergent strabismus developed; spasticity and contractures of all extremities gradually developed; episodes of rage and silly laughter	Two brothers similarly afflicted
Bischoff [20g]	1902	2 M	10 yr.	30(?)	20(?)	Stiffness of lower extremities began at age of 10 in both brothers; from age of 15 they were bedfast; intelligence simultaneously impaired	Only these two brothers had the disease

Neurologic Examination	Pathologic Findings
Increased reflexes in upper extremities; markedly spastic gait; fair power in lower extremities; all parts could be moved, but slowly, owing to spasticity; tendon reflexes in lower extremities extremely active; no sensory changes	Motor cortex, internal capsule, basal ganglia, or medulla not altered; spinal cord involved with degeneration of lateral pyramidal tracts from lumbar to upper cervical region; rim degeneration of lateral and anterior columns from upper lumbar to upper cervical region; slight degeneration of anterior pyramidal tracts in upper thoracic region; slight degeneration of lateral cerebellar tracts in thoracic and cervical regions; degeneration of tracts of Goll—slight in lumbar region, more marked as one ascends, traceable to medullary nuclei
Patient at first showed nystagmus, pallor of optic nerve head, impaired hearing in right ear, monotonous and slow speech, occasional spontaneous laughter, kyphoscoliosis to right in cervicothoracic region, marked ataxia of extremities, intention tremor, trunkal and head ataxia, increased patellar and triceps reflexes No paralysis, weakness or sensory changes noted Patient later showed more marked nystagmus, weakness of right internal rectus muscle, anisocoria, paraparesis; finally, marked optic atrophy, pupillary abnormalities, oculomotor palsies, and mental disorder	No abnormalities in brain, medulla or pons; sclerotic areas scattered irregularly and asymmetrically in lateral and anterior columns of spinal cord; none seen in gray matter or posterior columns
Intelligence severely damaged Bilateral ptosis; horizontal nystagmus; bilateral oculomotor nerve paralysis; anisocoria; pupillary reaction slow to accommodation, not to light; right optic atrophy; monotonous, slow, scanning speech; coarse tremor of head, tremor and incoordination of upper extremities, such that he no longer could write Walked only with help; gait unsteady, with wide base; slight increase in tone of muscles of lower extremities; slight contracture of thigh adductors; patellar, testicular, and abdominal reflexes very lively; Achilles reflex weakly obtained	No changes observed in brain, pons, or medulla Spinal cord: Microscopic sclerotic foci in posterior columns of cervical region Macroscopic sclerotic foci involving anterior two-thirds of lateral columns (but also here and there in anterior columns) of the thoracic portion; most marked changes about rim of cord; wedge-shaped area of demyelination in midpart of left lateral column and two small asymmetrical foci in anterior columns of lumbar portion Anterior and posterior roots: nests of atrophic fibers Peripheral nerves: Similar, but severer, changes
Nystagmus; slow speech; wasting of muscles in upper extremities In grasping objects, athetotic movements noted in upper extremities; later referred to as intention tremor and ataxia of the upper extremities Lower extremities: muscles wasted, paralyzed; legs crossed at knees, feet turned inward when he was held up; contractures of muscles; reflexes normal Touch, pain, and temperature perception intact throughout	Atrophy of corpus callosum Cerebral cortex: Little change in cortical cells, but reduction of fibers noted; white matter seemed diminished throughout Cerebellum: Marked reduction of fibers in white substance; Purkinje cells severely reduced in number Brain stem: Reduction in number and size of fibers of white matter; cells well preserved Spinal cord: Symmetrical lesions destroying chiefly direct cerebellar tracts and portions of posterior columns; general reduction of fibers in their size and number; cells of Clarke's columns destroyed Diagnosis: Severe hypoplasia of cerebrospinal axis, with predominance of lesions in white substance without any focal sclerosis, resembling Pelizaeus' case
Optic atrophy noted at age of 6 Nervous tremor on walking; gait rapid; speech markedly disturbed; touch and pain perception intact; bilateral optic atrophy and disseminated choroiditis; generalized convulsive attacks; reflexes in lower extremities of usual vigor Patient finally became bedfast, with contractures of lower extremities, and psychotic	Enlarged lateral ventricles; granulations on ventricular surfaces; softening of tip of left temporal lobe; various other gross changes; general atrophy of brain; external and internal hydrocephalus; chronic leptomeningitis; atrophy of cortex of frontal lobes emphasized Degeneration of lateral pyramidal tracts of spinal cord shown microscopically
Nystagmus on lateral gaze; tremor of tongue; intention tremor of extremities; no change in muscle tone or volume in lower extremities; walked with widened base and short, quick steps; unsteady Patellar reflexes increased, more so on left Intention tremor and broad, unsteady gait remained; transitory convergent strabismus; intelligence impaired Scarlatina; beginning of seizures; status epilepticus; death	No significant gross changes noted in cerebrum, cerebellum, or brain stem Spinal cord: In lower two-thirds of thoracic region and in lumbar region, pia-arachnoid opaque, milky-white; diagnosis leptomeningitis chronica spinalis Microscopic examination showed leptomeningitis increasing in severity from above downward; in lower thoracic region, slight loss of fibers at margin of lateral columns; in middle and upper thoracic regions, slight loss of fibers in tracts of Goll, but less in lateral columns; in middle and upper cervical regions, loss of fibers in small zone between Goll's and Burdach's columns and slight loss of fibers in most peripheral part of Gowers' bundle and lateral cerebellar tracts
Idiocy; intermittent convergent squint, worse on right; slight nystagmus; upper extremities spastic, partially flexed, and pronated; patient unable to stand; little voluntary movement of lower extremities; reflexes slightly increased; sensory system could not be evaluated	Cerebral hemispheres grossly intact; cerebellum generally atrophic; pons atrophic Spinal cord: Cervical level: Slight dilatation of central canal; reduction of fibers without sclerosis in region of anterior pyramidal tracts, but more involvement of crossed pyramidal tracts; slight reduction of fibers in anterior portion of posterior columns Sixth thoracic level: Same changes Lumbar level: No conservation of fibers in zone bordering lateral columns and in cerebellar tracts
From age of 25 to 27: "Tetanic rigidity" of lower extremities; clonic reflexes; increased tone of musculature of trunk, neck, and upper extremities; slowness and weakness in moving tongue and facial muscles, with stuttering speech Mobility of lower extremities markedly reduced; upper extremities weak, as was neck; back and abdominal muscles poorly mobile; no muscle wasting; eyeballs moved fully; touch sense intact; pinprick not perceived up to the head Intelligence degraded, yet patients were able to give adequate information about illnesses	Moderate enlargement of lateral ventricles; possible reduction in number of Betz cells Medulla: Fibers of pyramidal tracts thin throughout and glial structure of inner half of pyramidal tracts increased Spinal cord: From lumbar region up, in increasing intensity, was reduction in number of fibers in lateral pyramidal tracts and loss of fibers of middle part of tracts of Goll; increasing in intensity from cervical to lumbar region, was reduction in number of large anterior horn cells Cervical region: Reduction of fibers in areas of Gowers' tracts and possibly of uncrossed pyramidal tracts

Name of Author	Year of Publication	No. of Cases and Sex	Age of Onset	Age at Death, Yr.	Duration of Illness, Yr.	Clinical History	Genetic Factors
Newmark [290]	1904	1 M	8 yr.	22	14	Patient well until age of 9, when he had "typhomalarial fever"; gait peculiar before, but worse after this illness At age of 11, double achillotomy At age of 13, still able to walk long distances without fatigue Died of tuberculosis	Seven of nine children had the disease; mother and father showed no abnormalities (Family O'Connor)
Strümpell [291]	1904	1 M	26 or 27 yr.	69	42 43	First difficulty noted was in use of left lower extremity; at age of 34, gait was obviously involved; by the age of 55, walked with canes	Family "Polster"
Kollarits [294]	1906	1 M	12 yr.	36	24	Gradual onset and steady progress of weakness of lower extremities; patient bedfast by age of 20	Family reported by Jendrássik (Deutsche Ztschr. Nervenh. 22: 444, 1902)
Newmark [291]	1906	1 M	Before 8 yr.	20	More than 12	At age of 8 yr., parents felt he was "somewhat stiff in knees"; progressive spastic weakness of both lower extremities	Seven of 9 children of one family afflicted (Family O'Connor)
Pellizzi [295]	1906	1 M	15 yr.	25	10	Patient somewhat mentally retarded; went to school until 10 yr. old but could not distinguish letters; began to have difficulty in walking at age of 15; at age of 20, became agitated, talkative, incoherent, aggressive, and impulsive; psychosis quieted in about 4 mo., but a year later severe agitated attack was followed by marked mental deterioration; paraparesis progressed Enteritis, difficulty in swallowing, and decubitus ulcers; patient died	Development of spastic paraplegia at age of 15 in 3 brothers; all mentally diseased, psychotic, or retarded
Merzbacher [299]	1908	1 ..	Before 1 yr.	21 or 22	21	Apparently, symptoms began in the early months of life and were gradually progressive; clinical diagnosis of multiple sclerosis	This family described before by Pelizaeus; four generations involved, with 12 afflicted members; all onset of disease in early months of life
Jakob [296]	1909	1 M	4½ to 5 yr.	12	7 to 7½	Patient healthy until he began to have trouble walking; progressive weakening of lower extremities with muscular rigidity; by age of 9, could not walk without crutches; died of bronchopneumonia, at age of 12	Progressive spastic paraparesis developed in 3 brothers between ages of 3 and 5

of Spastic Paraplegia Reported in the Literature—Continued

Neurologic Examination	Pathologic Findings
At age of 11: "Flexed hips, flexed knees, adducted knees, and double equinus"; walked on toes At age of 13: Knee jerks exaggerated; "slight ankle clonus"; active abdominal and cremasteric reflexes; reflexes of upper extremities and jaw increased; no loss of power in lower extremities; no sensory changes	Motor cortex, internal capsule, pons, and medulla apparently normal Spinal cord: Degeneration of lateral pyramidal tracts first in sacral region, continued as far as lower portion of cervical region; no changes noted above this level; degeneration of medial portion of posterior columns began in midlumbar region and increased in degree of involvement up to their nuclei in medulla; apparent reduction in number of cells of Clarke's column
Patient examined many times between 1886 and 1900 Cranial nerves intact; sensation intact, although temperature sense uncertain late in life; reflexes "extraordinarily lively"; markedly spastic paraparesis of lower extremities, with hyperreflexia, ankle clonus, and occasional Babinski sign	Degeneration of lateral pyramidal tracts from lumbar to upper cervical region of cord; degeneration of rim of spinal cord, not significant; slight degeneration of ventral pyramidal tracts in upper thoracic and cervical portions of spinal cord; little degeneration of lateral cerebellar tracts; degeneration of tracts of Goll from upper thoracic region to medulla; internal capsule and motor cortex apparently intact
Constant tremor of head, eyelids, upper part of body, and upper extremities; impaired hearing; nystagmus Speech disturbed, as was motility of jaw and tongue; wasting of muscles of upper extremities; impaired movements of upper extremities, active or passive, with contractures in flexion Could not sit up without support; scoliosis; marked wasting, contracture, deformity of lower extremities—paraplegic Increase in tendon reflexes throughout Sensation intact	Motor cortex, internal capsule, cerebellum, mesencephalon, pons, and medulla apparently normal Spinal cord: First cervical level: Lateral pyramidal tracts stained lighter than normal, as did tracts of Goll, changes being symmetrical on two sides Midcervical level: Lighter staining of lateral pyramidal tracts; tracts of Goll just barely lighter Lower cervical level: Definite loss of fibers in lateral pyramidal tracts; Goll's tracts still stained lightly Thoracic, lumbar, and sacral portions: Symmetrical loss of fibers of lateral pyramidal tracts Peripheral nerves intact Fatty infiltration and reduction in size of muscle bundles
At age of 8: Gait not "evidently spastic, but knees tended to knock" Knee jerks considerably exaggerated; slight ankle clonus; superficial reflexes very active; abdominal muscles slightly rigid; reflexes "lively" in upper extremities; active jaw jerk Later: Spastic gait, hyperactive tendon reflexes, ankle clonus, and Babinski sign Deep and superficial sensation undisturbed	Cells of motor cortex, cerebellum, cells of Clarke's column, anterior horn cells, and spinal cord roots intact Sacral region: No changes Transition of sacral and lumbar regions: Suggestion of involvement of pyramidal tracts Lower lumbar level: Lateral pyramidal tracts involved on both sides, unequally Lumbar swelling up through brain stem: No changes noted in pyramidal tracts 10th thoracic level: Slight changes first noted in columns of Goll 7th cervical level: Degeneration of distal two-thirds of Goll's tracts, but even here some fine fibers remained in degenerated areas 4th cervical level: Dorsal half of Goll's tracts degenerated; degeneration continuing into medulla, where it occupied a triangle in medial portion of posterior columns near periphery
At age 22: Paraparesis in extension; equinovarus position of feet; deep reflexes markedly increased and bilateral ankle clonus; some cerebellar ataxia noted in lower extremities with spasticity; slight wasting of muscles throughout; early optic atrophy At age 24: Progressive atrophy of muscles of lower extremities, with impaired electrical reactions and reduced reflexes	Cerebral cortex: Diminution in number of neurones and fibers, especially in frontal lobes; various cell changes noted, mostly of chronic type; yellow-brown pigment in large and medium-sized pyramidal cells; Betz cells not reduced in number, but showing chromatolysis; no changes in cortical vessels Cerebellum: Purkinje cells shrunken and chromatolytic Internal capsule and brain stem: Reduction in motor fibers throughout these structures Spinal cord: Pyramidal pathways, both crossed and uncrossed, sclerotic throughout entire length down to lumbar region; similar lesions in tracts of Lissauer, Flechsig, and Gowers; demyelination of column of Goll in upper third of thoracic portion and in cervical portion; peripheral chromatolysis of anterior horn cells, especially in lumbar region, with cellular changes in posterior horns and Clarke's column Demyelination of anterior roots, especially at lumbar level; partial demyelination of posterior roots Sacral ganglia chromatolytic Right retina with chromatolysis of large ganglion cells
Tremor of head, nystagmus, ataxia, bradylalia; spastic paraplegia; sensory system intact; normal electrical reactions of nerve and muscle; sphincters unaffected	Loss of myelin sheaths (aplasia) of cerebral white matter, corpus callosum, and cerebellum; small areas of preserved myelinated fibers here and there in these demyelinated areas Preserved myelinated fibers in internal capsule, cerebral peduncles, pons, and medulla Brain: Myelination intact in narrow border between cortex and white matter; some axis-cylinders in atrophic areas; mild gliosis replacing destroyed nerve fibers; cortical cells intact Spinal cord not examined
Age 12: Mental retardation; imbecility; docility Cranial nerves intact Marked spastic paraparesis with contractures of thigh adductors, genuvalgum, and equinovarus Could not walk; no wasting of muscles of lower extremities Could move feet and legs for a short distance with normal strength, but with difficulty because of rigidity of muscles; passive movements impossible for same reason Cutaneous sensibility intact, but little impairment of position sense in lower extremities Knee jerk and ankle jerk hyperactive, with bilateral ankle clonus and signs of Babinski and Strümpell; cutaneous reflexes abolished; sphincters functioning well Upper extremities showed exaggerated tendon reflexes, but were otherwise normal On standing, position more insecure with eyes closed	Corpus callosum: One-third normal thickness Pre-Rolandic cortex, especially paracentral lobule: Atrophy of Betz cells; varying changes leading to cell sclerosis Brain stem: Both pyramids pale and atrophic, due to loss of fibers; same, but less intense, change in Gowers' tracts, and rubrospinal tracts; even less severe change in lateral cerebellar tracts; some pallor of fibers in reticular formation Spinal cord: Symmetrical degeneration of crossed pyramidal tracts, Flechsig's and Gowers' tracts, and, to less extent, anterior pyramidal tracts; some fibers missing in rubrospinal tracts and anteromarginal zone, extending throughout entire cord, more marked in thoracic region; slight thinning of Goll's tracts; definite gliosis about remaining intact fibers in degenerated tracts; cells of anterior and posterior horns intact; walls of blood vessels in zones of degeneration somewhat thickened; considerable atrophy of about one-third cells of Clarke's column; no loss of fibers in erural and sciatic nerves Intervertebral ganglia normal

Name of Author	Year of Publication	No. of Cases and Sex	Age of Onset	Age at Death, Yr.	Duration of Illness, Yr.	Clinical History	Genetic Factors
Raymond and Rose [290]	1909	1 F	12 yr.	27	15	Illness began with weakness of lower limbs, but course not usual	One sister began to have trouble with lower extremities at age of 9
Newmark [297]	1911	1 M	7½ yr.	31	23½	Illness began with stiffness of lower extremities; by age of 9, he had to use crutches; apparently difficulty in use of lower extremities got worse rapidly in the beginning and then remained much the same for years; syphilis at 25	Family O'Connor
Lederer [297]	1912	1 F	2 to 4 yr.	11	7 to 9	Gradually, between ages of 2 and 4, rigidity of lower extremities, speech disturbances, and abnormal movements of head and upper extremities developed; child died of severe erysipelas	Two younger brothers similarly involved
Schaffer [298]	1922	1 M	3 yr.	28	25	Trouble with walking gradually progressive; gait soon spastic, so that legs were together and patient had to walk on toes; at age of 17, beginning of impaired vision and trouble with speech	Another brother afflicted
Schaffer [291]	1926	1 M	3 yr.	38	35	Spasticity first noted in feet; weakness and stiffness spread upward slowly into upper extremities	Brother similarly afflicted
Paskind and Stone [10]	1933	1 M	At birth	11	11	Noted very early in life that child was not active, did not smile, cried very little; was always rigid; began to walk at 7½ years Gait awkward and spastic; upper extremities always stiff and awkward Never talked; had convulsive seizures from age of 2; incontinence of bowel and bladder	Two brothers similarly afflicted; one brother and sister appeared normal
Kahlstorf [295]	1937	1 M	31 yr.	63	32	Illness began with weakness of both lower extremities, gradually progressing to paraplegia; 16 years after onset some urinary difficulties developed	Eleven afflicted in family of 17, reported by Specht (Ztschr. Neurol. u. Psychiat. **99**:32, 1925)
Farago [9]	1947	1 M	14 yr.	42	28	Slowly progressive weakness of both lower extremities, so that by age 40 lower extremities were completely paralyzed; disturbances in urination and defecation; impaired sensibility to pain below umbilicus; rapid development of large decubiti, but they healed rapidly Death from septicemia	Eight afflicted members in 3 generations; other members of family showed neurologic or psychic changes; patient had monozygotic twin who had same symptoms as he did, but who committed suicide at age of 35

of Spastic Paraplegia Reported in the Literature—Continued

Neurologic Examination	Pathologic Findings
Age 14: Spasticity of lower extremities, more on left; weakness of extension of left leg, but when lying down she moved her lower extremities well; on standing, left thigh and leg slightly flexed and left foot in equinovarus position; yet patient walked easily Tendon reflexes very exaggerated, no ankle clonus	Although slight pallor at periphery of spinal cord in myelin stains, authors considered it no more than they had seen in normal cords; insisted that pyramidal tracts were intact from top to bottom Nothing abnormal found in motor cortex, internal capsules, cerebral peduncles, cerebellum, pons, and medulla
Age 15: Torticollis developed	
Age 16: Operation on neck muscles; no effect on torticollis	
Age 17: Feet in marked equinovarus position; could not walk without help	
Age 22: Double tenotomy because equinovarus position was so bad; patient could walk better	
Age 25: Pulmonary and peritoneal tuberculosis	
Age 26: Signs of Babinski, Oppenheim, and Strümpell	
Age 27: Motor condition more nearly normal	
Patient not examined in last six years of life; when last examined, had severe spasticity of lower extremities, intense spasm of adductors of thighs, could walk only with crutches, yet had good strength in muscles except when in contracture	Brain stem and cerebellum: No abnormalities; reduction in number of giant cells of Betz in paracentral lobules
Reflexes increased in upper extremities, but no change in power or tone of muscles; position sense in large toes always normal; diminution in touch, heat, cold, and pain perception in legs evanescent; one month before his death, return of feeling in legs to normal	Spinal cord: Demyelination of lateral pyramidal tracts first noted in the lower portion, continuous upward until it faded out in the upper cervical region, most marked in thoracic region; changes in posterior columns first noted at lower lumbar levels, with increasing involvement as one went upward, so that at C_4 only columns of Goll were involved; demyelination of Goll's tracts traced to gracile nuclei in medulla; rather spotty changes throughout anterior horn cells; no changes in other areas of spinal cord; posterior roots unaltered Spinal ganglia not abnormal
Markedly spastic paraplegia with hyperreflexia; ataxic-choreic movements of upper extremities and head; nystagmus in all directions of gaze; slight internal strabismus; partial optic atrophy; speech dysarthric, slow, and effortful; masticatory movements of jaw sluggish; weakness in closing eyelids	Grossly, brain normal and spinal cord "atrophic" Microscopically, defect in cells and fibers of brain and spinal cord; many undeveloped forms of nerve cells Authors thought this widespread arrest of development of nervous system
Horizontal nystagmus on lateral gaze; anisocoria; scanning and hesitant speech; slight hypertonia in muscles of upper extremities, but movements free; marked spasticity of muscles of lower extremities; equinovarus position of feet; inability to move feet; movements of legs and thighs slow and difficult; knee jerks exaggerated; bilateral Babinski and Oppenheim signs Sensory system intact	Slight demyelination of both lateral pyramidal tracts, beginning in upper thoracic region of cord and extending downward; slight demyelination of Goll's columns, beginning in upper thoracic region and continuing upward to nuclei in medulla Alzheimer's neurofibrillar change noted in neurones of Layers III and IV of cerebral cortex, especially in anterior central gyri; Layer V spared in this process; considerable loss of giant pyramidal cells by chronic atrophy; lipid changes in neurones of precentral cortex, more marked in anterior horn cells and spinal ganglia neurones Spinal ganglia neurones fenestrated, with diffuse neuronophagia No glial changes noted
No sensory or bladder disturbances Half-year before death, wasting muscles—slight in intrinsic muscles of hands, severe in triceps and tibialis anticus muscles; this, with spastic quadriparesis, gave picture of amyotrophic lateral sclerosis Temporal pallor of optic nerve heads and central choroiditis Tremor of head and hands Mentality intact	Spinal cord: Degeneration of both lateral pyramidal tracts from thoracic level down; from thoracic cord up diffuse degeneration of columns of Goll; swelling and early neuronophagia of anterior horn cells Motor cortex: Simple loss of giant Betz cells chiefly in leg centers; lessening of medium and large elements of pyramidal layer by neuronophagia Other cerebral cortex: Dysplastic cells in Layers III and V, slightly in VI (some cells with double nuclei); abnormal swellings of apical and basal dendrites of ganglion cells in Layers III and VI; granular degeneration of neurofibrillae; Alzheimer's fibrillary changes predominantly in cells of Layer III Spinal ganglia: Surprising number of dysplastic cells and Cajal's *celula fenestrada*, with subcapsular satellite proliferation
Scissors gait; spastic paraparesis; tone and reflexes markedly increased in muscles of lower extremities; bilateral Babinski signs and ankle clonus; abdominal and cremasteric reflexes absent; movements of upper extremities awkward and reflexes here variable Sensory reaction to pinprick throughout Idiocy	Microcephaly Undeveloped myelination, chiefly in white matter of occipital and parietal lobes Deposition of islands of gray substance in white matter of brain (heteropia); cerebral agyria, pachygyria, and microgyria Brain stem and spinal cord intact
No changes in cranial nerves, although movements of tongue and jaw impaired; deep reflexes slightly increased in upper extremities; abdominal reflexes weak; patellar reflexes exaggerated; Babinski sign on left, equivocal on right because of old deformity of right foot; equinovarus deformity of feet; spastic paraplegia; no sensory changes; sensorium clear	Degeneration of pyramidal tracts, especially lateral columns; degeneration of both columns of Goll; degeneration of lateral cerebellar tracts; hypoplasia of cerebellum; atrophy of basal ganglia; reduction of number of giant pyramidal cells in anterior central gyri
Musculature of both lower extremities somewhat atrophic, emaciated, and hypertonic; patellar and Achilles reflexes increased bilaterally; bilateral patellar and ankle clonus; equivocal Babinski sign; abdominal reflexes obtained; consciousness clouded, somnolent, dazed	Severe changes in neurones of precentral gyri: Swelling with increased pigmentation, shrinkage, various degrees of neuronophagia with complete disappearance of neurones, neurofibrillae thickened; marked reduction in number of neurones in Layers III and VI, especially Layer V, of precentral gyri; apparent reduction in number of Betz cells; myelinated fibers of supraradial and zonal layers damaged Pyramidal tracts involved in medulla oblongata, but much more in spinal cord; demyelination somewhat in tracts of Goll, Flechsig, and Gowers; changes in neurones of Clarke's column and of spinal ganglia

It should be remembered that the pyramidal tract is very susceptible to damage in many disease processes. Brouwer [32] has tried to explain this on the basis of a physicochemical difference of this tract because of its rather late phylogenetic appearance. Others have suggested that the tremendous length of the tract alone may constitute the basis for its susceptibility. Lassek [31] has summarized his views on the pyramidal tracts as follows:

> The long length of their fibers, their large area with many neurons of variable diameters, their position, their splitting into subdivisions and their vascular supply by all the blood vessels coursing to the central nervous system are such that, other factors being equal, they can be involved by lesions situated in any part of the brain or cord.

Too much emphasis on the corticospinal tracts in this condition may be fallacious. Indeed, some pedigrees have been described under the title "familial lateral sclerosis." Recent advances in the physiology of the motor divisions of the central nervous system indicate that spastic paraplegia is not the result of damage to, or destruction of, the pyramidal tracts alone. Spasticity represents involvement of extrapyramidal pathways.[33] In the spinal cord of a patient reported as having family spastic paraplegia which I have had a chance to examine, the greatest change was in the ventral funiculi, while other extrapyramidal pathways were also somewhat involved. Such damage would explain the well-marked spasticity in the present cases, a spasticity which is increased on the patient's attempting to stand or walk, with disproportionate loss of voluntary power.

In this connection, we must realize that the older pathologic studies lacked anatomic and physiologic knowledge we now possess. For instance, the location of lower-extremity motor neurones in the paracentral lobule and vertex of the precentral area was not fully appreciated until recently.[34] Any study of the motor cortex, to be thorough, would require careful studies of these areas, in contrast to the middle and lower portions of the precentral gyrus. Anyone who has followed the careful studies of Lassek [31] must realize how inadequate previous pathologic studies in hereditary spastic paraplegia have been. The exacting techniques devised by Lassek to study the Betz cells and the fibers of the pyramidal tracts must be applied to future studies of pathologic material in this condition. Only with such zeal and scientific exactitude can we hope for better clinicopathologic correlations in this disease or in related diseases.

In the literature, one can find many studies which show that different neurologic syndromes have been found in one family, or even in the same generation of one family.[35] Garland and Astley [36] reported a family in which spastic paraplegia, amyotrophy, and pes cavus occurred as a dominant inheritance. Landau and Gitt [37]

32. Brouwer, B.: The Significance of Phylogenic and Ontogenic Studies for the Neuropathologist, J. Nerv. & Ment. Dis. **51**:113-136, 1920.

33. Fulton, J. F.: Physiology of the Nervous System, Ed. 3, New York, Oxford University Press, 1949, p. 420.

34. Rasmussen, A. T., and Penfield, W.: Further Studies of Sensory and Motor Cerebral Cortex of Man, Federation Proc. **6**:452-460, 1947.

35. Spillane, J. D.: Familial Pes Cavus and Absent Tendon Jerks: Its Relationship with Friedreich's Disease and Peroneal Muscular Atrophy, Brain **63**:275-290, 1940.

36. Garland, H. G., and Astley, C. E.: Hereditary Spastic Paraplegia with Amyotrophy and Pes Cavus, J. Neurol., Neurosurg. & Psychiat. **13**:130-133, 1950.

37. Landau, W. M., and Gitt, J. J.: Hereditary Spastic Paraplegia and Hereditary Ataxia: A Family Demonstrating a Variety of Phenotypic Manifestations, A. M. A. Arch. Neurol. & Psychiat. **66**:346-354, 1951.

reported a large family through seven generations (283 persons) in which 21 members were disabled by a progressive neurologic disease. The most uniformly occurring disorder was due to degeneration of the pyramidal tract, but cerebellar, anterior-horn-cell, and "striatal" symptoms and signs, too, were variably mixed in these cases. Again, the paraplegia or paraparesis was used as the pivotal point on which classification was made. This phenotypic inconstancy is presumably due largely to genetic factors (modifiers), but other biologic factors, acute or chronic, may help to produce such clinical variability.[37] As Spillane [35] said:

> Clinical designations are artificial in that they refer only to a selected group of symptoms and signs produced by a more widely distributed underlying pathological process. It is this process alone that can be called a disease.

Yet in my experience I have seen cases in which the motor system alone was involved, the process progressing slowly and the end-result after decades being limited to the motor system only. While I agree in substance with Spillane, I still feel it wise to classify and consider separately those manifestations which appear to be inherited as a distinct clinical entity and to constitute a relatively constant syndrome ("pure form"), for these forms seem to offer a better starting point for biologic and genetic investigations.

Into the discussion of hereditary spastic paraplegia must eventually come a consideration of the sporadic cases, those of "primary lateral sclerosis." Wechsler and Brody [38] attempted such a study. It is not an uncommon experience to find cases in which the initial picture is spastic paraparesis or paraplegia, only to have the patient later exhibit other signs and symptoms, indicating the true cause of the disorder. But there is also the patient with only spastic paraparesis or paraplegia, in whom repeated studies reveal no etiologic factor and in whom after many years the only findings are those of pyramidal-extrapyramidal disease, involving mostly or only the lower extremities. Are these sporadic cases instances of hereditary spastic paraplegia in which the siblings do not live long enough to manifest the disease, so that its heredofamilial basis cannot be recognized? Certainly, the disease in the man in my second pedigree (Family Ec.) would have been considered "primary lateral sclerosis" if I had not known that his sister had the same condition. A similar question must arise about the spastic paraplegia which develops late in life. Often it is thought to be due to arteriosclerotic or senile degenerative causes. Yet some of these patients did not exhibit their symptoms until they were in the seventh decade of life. A report [39] in which several siblings had onset of their symptoms in the eighth decade has been recorded. It is certainly not possible to answer such speculations on the basis of the data available at present. More patients with sporadic spastic paraparesis or paraplegia need to be followed longer and more adequately studied pathologically before one can hope to answer these questions.

Bell [5] believed that Friedreich's ataxia and spastic ataxia were due to the same gene or genes, perhaps influenced by modifiers. She was more doubtful with respect to spastic paraplegia. She believed that there were a recessive and a dominant form of these three diseases. A few cases she believed represented a sex-linked recessive type of inheritance. From her studies, she claimed a common genetic basis

38. Wechsler, I. S., and Brody, S.: The Problem of Primary Lateral Sclerosis, J. A. M. A. **130**:1195-1198, 1946.

39. Giovanardi, A.: Riforma med. **12**:754, 1897; cited by Price.[4]

for spastic paraplegia, Friedreich's disease, and spastic ataxia. Haldane,[40] using her data, concluded that these three conditions were not due to the same gene. He concluded that recessive spastic paraplegia was due to a partially sex-linked gene. Dominant spastic paraplegia was thought to be due to an "autosomal" gene. He further suggested that the different ages of onset are determined by three or more allelomorphs of the partially sex-linked gene. My first family, at least in its first four generations, suggested a dominant inheritance; in the fifth and sixth generations sex-linkage seemed probable. The nonappearance of diseased members in the later generations of this family may be only apparent now and need not suggest a dying out of the disease process. The second family did not give any indication of the genetic background. The third family suggested a recessive inheritance, while the fourth suggested a dominant type of inheritance. I believe that in the future genetic analyses should be more discriminating in their selection of cases. For instance, in my opinion Bell's [5] inclusion of Paskind and Stone's [10] family was totally unwarranted on both clinical and pathologic grounds.

SUMMARY

The pedigrees of four families whose members have shown spastic paraparesis or paraplegia are reported. This study included the histories, neurologic examinations, and laboratory studies of 12 diseased members of the 32 persons said to have been afflicted in these families.

The pathologic findings in the spinal cord in a case formerly reported clinically by Bayley and Spiller are described. Demyelination of the corticospinal tracts and certain of the extrapyramidal pathways in the spinal cord was observed.

An attempt is made to suggest the direction of future pathologic studies of such cases as these on the basis of newer anatomic and physiologic knowledge and more precise histopathologic techniques.

40. Haldane, J. B. S.: Partial Sex-Linkage of Recessive Spastic Paraplegia, J. Genetics **41**:141-147, 1941.

EARLY STAGE OF SCHILDER'S DISEASE AND RELATION TO OTHER FORMS OF LEUCOENCEPHALOMYELITIS

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SINCE Schilder's description of "Encephalitis periaxialis diffusa," the study of a fairly great number of cases has led to the general acceptance of this histologically well-characterized picture as an early stage of diffuse sclerosis. It is evident that for elucidation of the pathogenesis of this disease knowledge of its early stages is required. So far only a single case with a fulminating course and fatal outcome has been described (Case 3 of Stewart, Greenfield, and Blandy[1]). The case to be reported here was characterized also by a fulminating course and seems important to the general aspect of the pathogenesis and classification of Schilder's disease.

REPORT OF A CASE

A. K., a woman born Sept. 12, 1929, a tailor's apprentice, was admitted to the department of neurology and psychiatry on Jan. 31, 1950. The family history, taken from her brother-in-law, revealed nothing relevant to her present illness. Her somatic and mental development was normal. She had never before been seriously ill.

About Jan. 20 she caught a cold. On Jan. 23 an urticaria-like rash appeared on her face and body, disappearing after a few days. Thereafter she was free from complaints. On Jan. 27 she gave the impression of being nervous and slept restlessly. The following day she was somnolent, had to be fed, and vomited. She had no complaints but was reluctant to speak. Since then she had become increasingly stuporous.

On admission the patient appeared well developed and well nourished. No exanthematous lesions were visible. The temperature was 37.5 C. (99.5 F.) on admission and rose to 38.5 C. (101.3 F.) by midnight. In the right gluteal region a few excoriations and bullae were visible. Physical examination of the internal organs did not reveal anything abnormal except for diffusely rough respiration. The pulse rate was 80 per minute; the blood pressure, 110/65. The pharynx and the tonsils were somewhat hyperemic. She coughed spontaneously and had a thick, grayish mucous sputum.

The blood cell count revealed 4,500,000 red cells, 87% hemoglobin, and 15,200 white cells. The sedimentation rate was 32 mm. in one hour. The urine contained traces of albumin but no other pathologic constituents.

There were no signs of meningeal irritation.

Neurologic Examination.—The eyelids were open. Conjugate spontaneous movements of the eyes in various directions without fixation were observed. The pupils were equal. The only remnants of ocular reactions were closing of the eyelids on very strong light stimulation and reactions of the pupils to light, both direct and consensual.

From the Department of Neurology and Psychiatry, University of Pécs Medical School.

1. Stewart, G. T.; Greenfield, J. G., and Blandy, M. A.: Encephalitis Periaxialis Diffusa: Report of Three Cases with Pathological Examinations, Brain **50**:1, 1927.

The patient being unconscious, examination of muscle power was impossible. The tonus was reduced in the lower extremities, while it seemed to be increased in the extensors of the right elbow and in the flexors of the left elbow. Tonic neck reflexes and support reactions could not be elicited.

The deep reflexes were symmetrically present; the abdominal cutaneous reflexes were absent. There was a questionable Babinski sign on the right, while on the left the plantar response was of the flexor type, only Gordon's sign being positive.

The patient was unconscious and made no spontaneous movements. Her posture was completely passive. Only strong thermal stimuli elicited weak defensive movements of the upper extremities and of the right lower limb.

Lumbar puncture yielded slightly bloody cerebrospinal fluid. The pressure was not increased. The fluid contained 4 lymphocytes per cubic millimeter; Pandy's test gave an opalescence, and phase 1 was negative. On the second lumbar puncture, on Feb. 1, a count showed 18 polymorphonuclear leucocytes, 12 lymphocytes, and 2 macrophages per cubic millimeter. The protein content was 24 mg. per 100 cc. The Wassermann reactions, both of the blood and of the cerebrospinal fluid, were negative; the fluid proved to be sterile on bacteriologic examination.

The blood cultures remained sterile.

The physical and neurologic findings remained essentially the same during hospitalization. The patient was in a continuous deep coma. Finally the deep reflexes disappeared. The temperature rose to 41 C. (105.8 F.) on Feb. 4, and the patient died the same day.

At autopsy the internal organs showed no gross morbid changes, except hypostasis of the lungs.

The surface of the brain presented no pathologic changes. The spinal cord was not examined.

On transverse section of the cerebral hemispheres, the central part of the white matter proved to be soft and of grayish color, much like that of the normal cortex, with some pink patches, the size of a pinhead. The altered tissue seemed to be everywhere sharply demarcated from the normal. In the frontal lobes, just anterior to the pole of the frontal horn, the lesions reached almost to the cortex, leaving intact only a narrow subcortical boundary. The pathologically changed tissue formed a large area in each hemisphere. The genu of the corpus callosum was altered in the same way in its entirety except for a narrow margin on the surface. Thus, the bilateral pathologically changed areas coalesced (Fig. 1 *A*). Farther anteriorly, the pathologic change receded more and more from the cortex, so that the normal-looking white matter became increasingly broader. In the occipital direction, the large lesions seemed to divide into several areas of various sizes, their diameters measuring from a few millimeters to about 3 cm. Such areas occupied the major part of the cut surface in the centroparietal region (Fig. 1 *B*). The temporal lobes, containing only a scanty number of smaller foci, were less damaged. In the occipital lobes, also, the morbid changes were mainly localized to the dorsal parts. In the corpus callosum behind the genu, the process spared first its central part and then progressively also the beginning of its radiations on each side.

The distribution of the lesions in the two hemispheres was fairly, but not entirely, symmetrical.

Histologic study was carried out with the usual techniques. The myelin preparations yielded a very conclusive finding, especially in those taken from the frontal lobes (Fig. 2). The centrum ovale was poorly stained almost in its entirety. There was a difference in the results of different myelin methods; the deficient staining was much more pronounced in the Loyez than in the Spielmeyer and Weigert-Kultschitzky preparations. This was mainly due to the affinity of myelin disintegration products for the hematoxylin. These products remained preserved in the frozen and chromated material, while alcohol and ether extracted them from the nonmordanted material to a significant degree. Thus, they were lost during the procedure of celloidin embedding which preceded the Loyez staining, and at most their scanty remnants were slightly colored in Loyez preparations.

The pale staining of the white matter beneath the cortex was sharply demarcated. The so-called U-fibers were generally preserved. The relative sparing of these U-fibers is one of the generally accepted, though not necessary, characteristics of diffuse sclerosis. In my preparations,

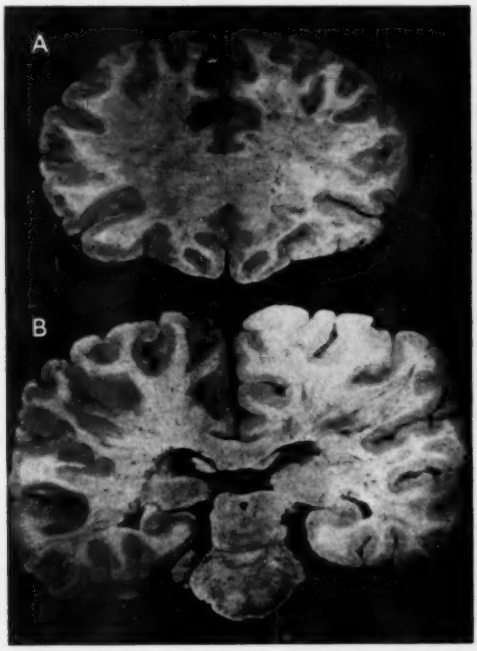

Fig. 1.—Coronal sections of the brain: *A*, section through the frontal lobes and rostrum of the corpus callosum; *B*, section through the central and temporal lobes, pulvinar, mesencephalon, and pons.

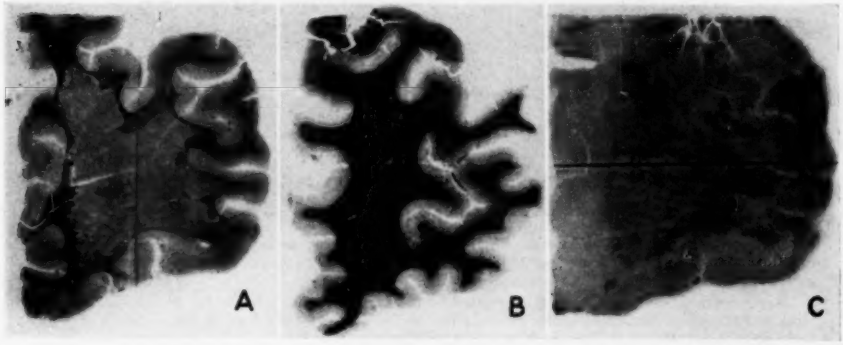

Fig. 2.—Transverse sections of the right frontal lobe. *A*, Loyez preparation; *B*, Spielmeyer stain; *C*, Nissl stain. *A* and *C* were from the same celloidin block; *B* was from the adjacent anterior one. In *A* a few preserved islets of myelinated fibers are seen within the compact area of demyelination. There are two small foci—one in the medial orbital gyrus; another in the middle frontal gyrus.

also, I found parts in which the demyelination involved the subgyral fibers (Figs. 2 and 3 *B*). Oftener, even a broader band than the layer of the U-fibers was spared. It should be emphasized that not only the U-fibers in the strict sense of the word, i. e., the intergyral systems, remained intact, but all fibers of the same layer were preserved.

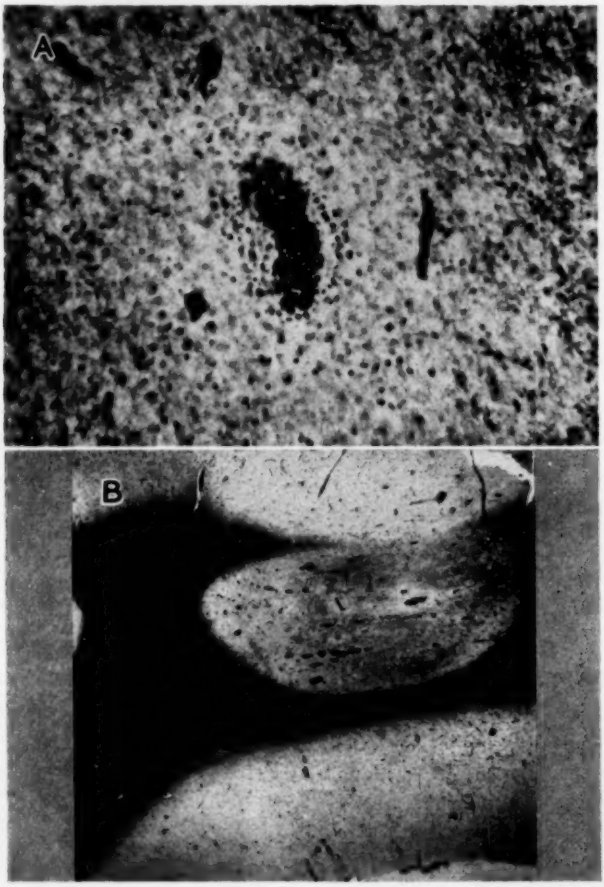

Fig. 3.—*A*, small central vessel filled with erythrocytes; around it is entire loss of the myelinated fibers. In a more distant zone a part of the fibers are still preserved, but poorly stained and irregularly outlined. Loyez stain.

B, subcortical lesion, apparently unrelated to the large demyelinated area; perivascular halos with a tendency to coalesce; sharp delimitation of the entire focus; loss of the U-fibers and, in the adjacent cortex, of the radial fibers. Loyez stain.

This subgyral sparing is not wholly understood. Schilder [2] took into consideration the difference in blood supply of the fibrae arcuatae and the deeper white matter. The subgyral layer

2. Schilder, P.: Zur Kenntnis der sogenannten diffusen Sklerose. (Über Encephalitis periaxialis diffusa), Ztschr. ges. Neurol. u. Psychiat. **10**:1, 1912.

receives vessels from the pia, whereas the rest of the white matter is nourished by branches of basal vessels. It seems probable to me that this difference in vascular supply plays a role in the peculiar delimitation, but does not offer a complete explanation. Such sparing of the subconvolutional fibers is also seen in processes other than diffuse sclerosis, as was mentioned by Steiner [3] and by Hallervorden and Spatz,[4] especially in vascular processes.

Thus, the large demyelinated area presented in its extension and delimitation the characteristics of Schilder's disease. But it was not evenly stained. On the whole, it stained gray, but was areolated with small patches of even poorer staining. These patches were round or elliptic, usually with a small blood vessel lying in their center. In the better-stained part, a number of pale-colored myelinated fibers were visible, often showing an irregular course and swellings. The small, almost unstained patches contained still less, if any, myelin sheaths (Fig. 3 *A*). A few small round or elliptic areas of demyelination were noted outside the large lesion, but always in the white matter, never in the cortex (Fig. 3 *B*). If the demyelination involved the arcuate fibers, it did not extend into the cortex; only the radial fibers were lost over the damaged medullary substance. Apart from that, the myelin architecture of the cortex seemed generally

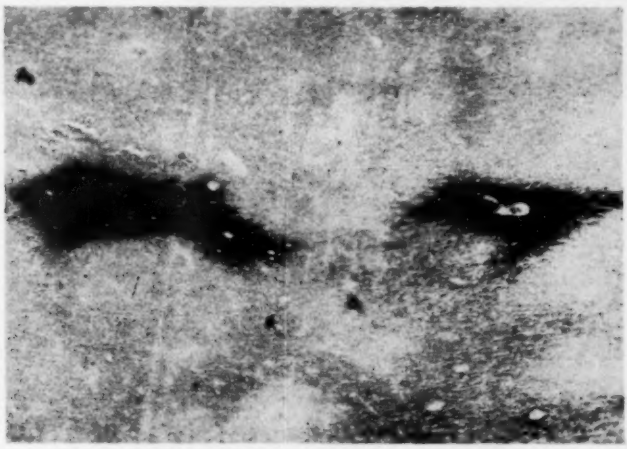

Fig. 4.—Preserved myelin islets; confluent perivascular halos.

unchanged. A few preserved myelin islets were found in the large field (Figs. 1 *A* and 4). Serial sections prepared from some of them showed adherence to the intact white matter; whether this was true for all such islands cannot be ascertained.

The demyelinated area showed fairly sharp delimitation. The boundary, showing slight indentations, was not quite regular, as in the cases observed by Weimann [5] and Shelden, Doyle, and Kernohan.[6] The irregularities were often due to the expansion of the process in the form of small round or elliptic foci (Fig. 5), as in Case 3 of Stewart, Greenfield, and Blandy.[1]

3. Steiner, G.: Multiple und diffuse Sklerose, in Bumke, O., Editor: Handbuch der Geisteskrankheiten, Berlin, Springer-Verlag, 1930, Vol. 2, p. 289.

4. Hallervorden, J., and Spatz, H.: Über die konzentrische Sklerose und die physikalisch-chemischen Faktoren bei der Ausbreitung von Entmarkungsprozessen, Arch. Psychiat. **98**:641, 1933.

5. Weimann, W.: Zur Kenntnis der sogenannten "diffusen Hirnsklerose," Ztschr. ges. Neurol. u. Psychiat. **104**:411, 1926.

6. Shelden, W. D.; Doyle, J. B., and Kernohan, J. W.: Encephalitis Periaxialis Diffusa, Arch. Neurol. & Psychiat. **21**:1270, 1929.

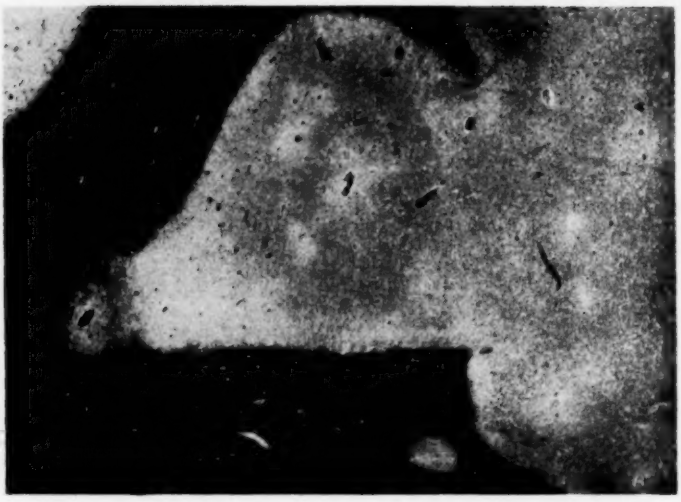

Fig. 5.—Edge of the demyelinated area in the medial orbital gyrus. The delimitation is somewhat irregular, owing to perivascular expansion of the process. In the lower part of the photomicrograph is an apparently independent small focus. Loyez stain.

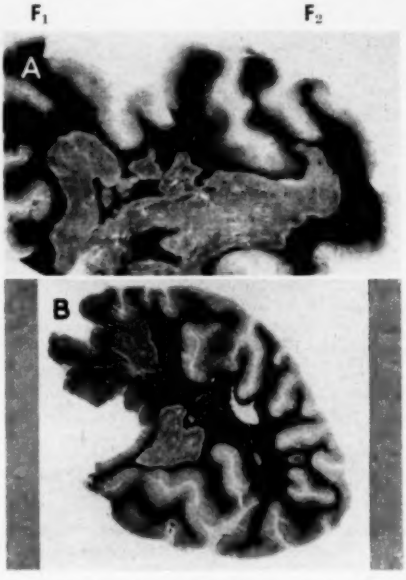

Fig. 6.—*A*, transverse section through the posterior part of the right frontal lobe. F_1, superior frontal gyrus; F_2 middle frontal gyrus. Note masses of spared myelinated substance within the huge demyelinated area and the longitudinal direction of the entirely pale foci, corresponding to the direction of the vessels. Spielmeyer stain.

B, right occipital lobe, showing two large and several small foci. Perivascular halos within the large lesions recognizable. Spielmeyer stain.

As one progressed toward the frontal pole, trabeculae of the intact white matter were seen to enter the demyelinated field, dividing it into smaller and larger areas, which had no, or only slight, connections with one another. The same conditions could be observed in the occipital direction (Fig. 6*A* and *B*). In sections through the head of the caudate nucleus the intact myelinated islands became larger, and the border of the demyelinated area receded from the cortex. More posteriorly, the centrum ovale contained separate large and small demyelinated areas. The process invaded the upper part of the internal capsule, reaching, but fairly exactly respecting, the borders of the basal ganglia. Demyelination extended into the right external capsule, at some levels down to its basal part. This lesion kept itself to the lateral margin of the putamen. A small focus was observed in the capsula extrema on the right side.

The central part of the anterior commissure was demyelinated. This lesion extended first symmetrically to the two sides, but did not spread into the radiations and remained fairly within the border of the commissural bundle, transgressing it only on the right for a small field into the globus pallidus. In this structure, another slightly affected area was observed at the dorsal edge (Fig. 7).

Fig. 7.—Transverse section showing the extent of demyelination in the anterior commissure on the right side. The fibers of the globus pallidus over the commissure and in the dorsolateral edge, and the uppermost part of the internal capsule are poorly stained, owing to myelin disintegration. Spielmeyer stain.

The isolated damaged areas generally had sharp border lines, like the foci in multiple sclerosis. Exceptions were chiefly the small perivascular foci, the contours of which were usually less distinct.

The breakdown of the myelinated fibers was not everywhere complete. In some places even their direction was recognizable, although they showed only pale staining and the presence of disintegration products. Such areas as were present in the stratum subcallosum and at the collection of the corona radiata fibers into the internal capsule reminded one of the so-called shadow plaques, known in the pathology of multiple sclerosis.

Bielschowsky preparations of frozen sections showed definite loss of axis-cylinders. This process did not show quite the same intensity as that of the myelin sheaths. Many of the remaining axis-cylinders appeared normal, while others were slightly altered, presenting an irregular course and circumscript spindle-like swellings.

In Sudan preparations an immense number of fat-laden scavenger cells were seen in the damaged areas. However, they were never closely packed, but, rather, were scattered even when they were present in large numbers. Most of these cells were noted in the immediate vicinity of of the vessels; farther away their number decreased. Thus, it became clear that the poor staining of the myelin preparations was due to the disintegration of the myelin into less complicated fatty substances. A comparison of the myelin preparations with those stained for fats justified the conclusion that different stages of lipid disintegration (prelipid and lecithinoid, neutral fats), were present. Compound granular cells were always found only in the nerve tissue. The fat granules were, as a rule, exceedingly fine. It was interesting that the fat-laden cells lying close to the vessel walls were often flattened, almost spindle-like, instead of the usual round form. Fat-laden oval or spindle cells were visible in some places, where the direction of the fibers seemed to determine their shape. Sometimes the endothelial cells of the small vessels enclosed tiny fat granules. In the foci of the occipital lobe, part of the myelin sheaths was swollen and stained red with Sudan III, while fat-laden scavenger cells seemed to be at a somewhat earlier stage of their development.

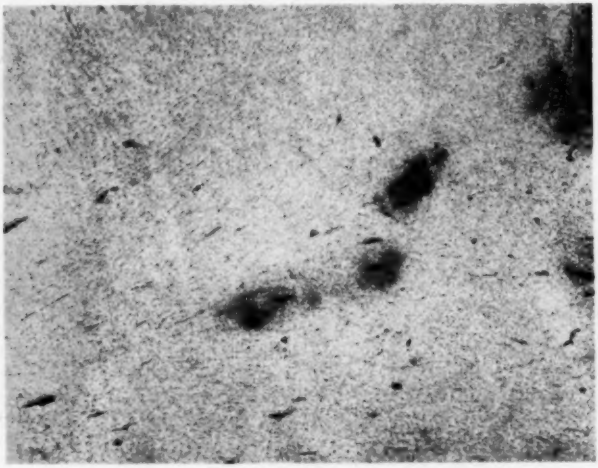

Fig. 8.—Tissue infiltration in the demyelinated area with very prominent perivascular accentuation. Nissl stain.

Although various fat products were found and the scavenger cells also showed somewhat differing maturity, there was no reason for regarding these differences as significant for the nature and developmental stage of the process. Thus, fat stains gave, in contrast to the negative picture of the myelin preparations, a positive one. The same held true for the Nissl preparations, in which the perivascular foci were already macroscopically recognizable by their deeper staining (Fig. 2*C*). Microscopically, the demyelinated field showed an abundance of nuclei, the density of which was mostly very pronounced around the small vessels (Fig. 8). The endothelial cells of the vessels were swollen and the adventitia was only slightly or not infiltrated (Fig. 9*B*). The infiltrations were formed mainly of lymphocytes and histiocytes. Fully developed plasma cells were also visible, but oftener the chromatin of lymphocytes was arranged in clumps, indicating transformation into plasma cells. A proof of the emigration of the hematogenous and adventitial elements was given by the presence of plasma cells in the nerve tissue. Neither in the adventitial nor in the tissue infiltrations were polymorphonuclear leucocytes, including eosinophiles, visible. The commonest elements in the infiltrated tissue were scavenger cells, the plasma of which usually showed a reticular structure. Some of the fully developed scavenger cells had

enormous dimensions, their plasma being 10 times as large as their nucleus. Various forms of scavenger cells, developing from the microglia, were visible. The neuroglia also showed moderate hypertrophic and hyperplastic changes. Amitotic and mitotic figures and binucleated scavenger cells and astrocytes were seen. The fibroblastic activity of the astrocytes was very modest (Holzer stain), as it corresponded to the early stage of the pathologic process.

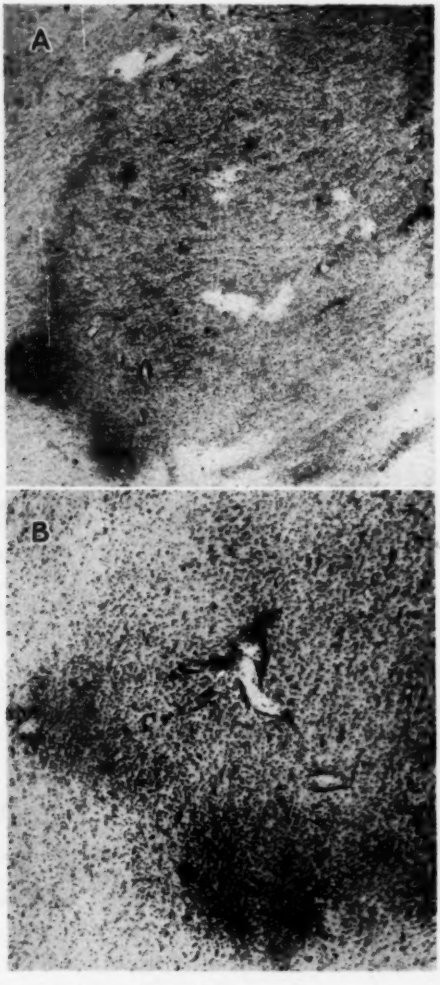

Fig. 9.—*A*, marginal part of the lesion of the internal capsule with wall formation. The gaps in the preparation are artifacts. Nissl stain.
B, a part of *A* under higher magnification.

The perivascular tissue infiltrations could be classified into two extreme types. One of them appeared as a rather loose cellular gathering, fading away with sharp limits into the neighboring

tissue. In the other type the infiltration was dense and fairly well defined. Its density was sometimes accentuated on the outer border, thus presenting a so-called wall formation. It was evident that the first type corresponded to the infiltration type visible in the parainfectious and postvaccinal encephalitides, while the other was known from acute multiple sclerosis. The first type was more rarely seen than the second, and sometimes it marked, on the margin of larger foci,

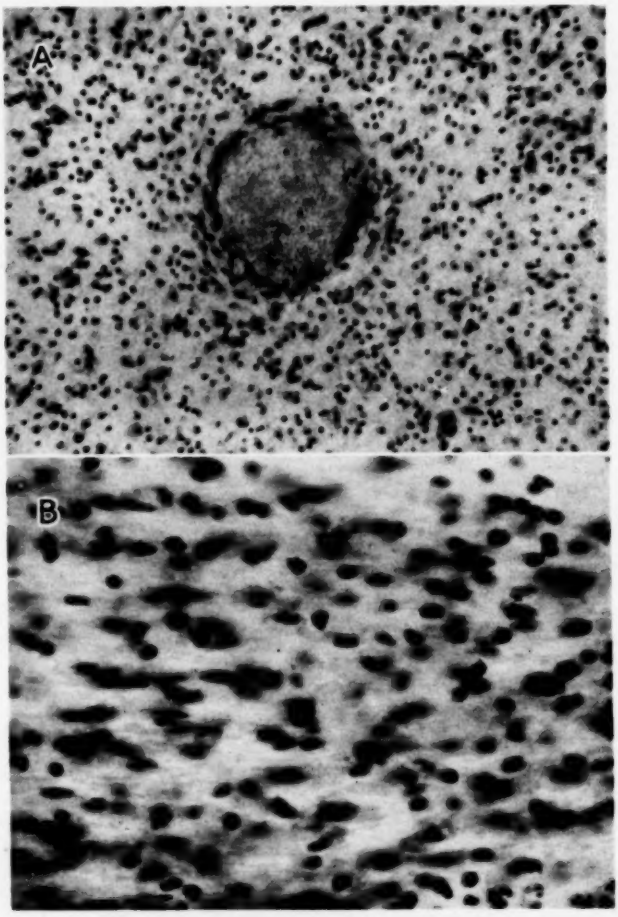

Fig. 10.—*A*, central vessel with slight infiltration in a part of the adventitia. In the vicinity is definite, but modest, tissue infiltration. Nissl stain.
B, longitudinal cells among the fibers of the internal capsule. Nissl stain.

the progress of the pathologic process. In some vessels the adventitial infiltration was very slight, or even missing; yet the tissue infiltration could be definite, though as a rule it was not very pronounced (Fig. 10 *A*). Such infiltrations were also met with in parainfectious encephalitis. Transitions between the various types were often seen.

The perivascular foci often coalesced, and the marginal part of the larger areas occasionally showed a tendency to wall formation (Fig. 9*A*). One of the remarkable histologic details was the presence of longitudinal cells in the affected part of the internal capsule (Fig. 10 *B*). A similar observation was reported by Siemerling and Creutzfeldt.[7] They considered this shape of the proliferated glial elements a result of accommodation to the direction of the nerve fibers. The Nissl preparations gave the impression that the longitudinal elements were also scavenger cells, a conclusion which was supported by the fat stains.

The observations made by means of the various histologic methods left no doubt that the larger demyelinated and infiltrated areas originated from the confluence of perivascular foci.

There were a few small perivascular hemorrhages. They were not essentially connected with the pathologic process, but developed during the agonal state. No thrombi could be recognized by means of nonspecific stains.

An outstanding feature of the present case was the pale border of the larger demyelinated areas, not yet described in the literature. This border, a few millimeters wide, appeared almost everywhere and was visible in preparations stained by any method. Being present also in unembedded sections, it could hardly be the result of artificial shrinkage. Nor was any loss of tissue visible, the myelin and fat preparations showing only rarefaction of the myelinated fibers. This rarefaction was most probably due to an edematous imbibition at the junction of the normal and the affected tissue.

Striking was the almost symmetrical extension of the morbid process in the two hemispheres. The optic nerves, examined at their origin from the chiasm, and the optic tracts proved to be normal.

The gray matter was free from foci. Cortical foci, frequently seen in multiple sclerosis, were not noted. Quite exceptionally, a slightly infiltrated vessel was met with far from the demyelinated area, where only slight perigliosis (Wohlwill) indicated abnormality. The ganglion cells were poorly stained everywhere in the gray matter, owing to loss of tigroid substance. This change might be ascribed to the agonal state and was thus independent of the essential process.

Preparations of the mesencephalon, pons, medulla oblongata, and cerebellum revealed no pathologic changes except for pale staining of the ganglion cells and some adventitial fat-granule cells.

The leptomeninges were edematous, and in some places slightly infiltrated by lymphocytes. Beneath the infiltrations, the superficial layer of the cortex presented glial proliferation.

The extension of the demyelination in the frontal lobes and the structural characteristics of the process in this case enable one to establish the diagnosis of Schilder's form of diffuse sclerosis. In more posterior parts of the hemispheres a number of seemingly or really isolated foci of differing sizes were visible. An examination of individual sections from these parts would lead to the diagnosis of multiple sclerosis. How far the apparently isolated, affected areas were prolongations of a central large lesion, as in some instances in the frontal lobes, cannot be ascertained, because serial sections have not been made of any portion of the hemispheres. This had not been planned, for I intended to prepare blocks for examination by various histologic methods. A connection, for example, between the small temporal foci and the large frontocentroparietal lesion is hardly to be imagined. The demyelination in the anterior commissure is also probably independent of any other pathologic area.

Of utmost importance is the finer structure of the demyelinated areas. As in Case 3 of Stewart, Greenfield, and Blandy, the large field, with the character of diffuse sclerosis, arises from confluence of small perivascular lesions. The same explanation of the process was given for cases of longer duration by Sheldon, Doyle,

7. Siemerling, E., and Creutzfeldt, H. G.: Bronzekrankheit und sklerosierende Encephalomyelitis, Arch. Psychiat. **68**:217, 1922.

and Kernohan,[6] and, further, by Waggoner and Löwenberg [8] in a case interpreted by them as one of concentric sclerosis.

The relation of multiple to diffuse sclerosis has been emphasized by several authors since Schilder's first publication. Foci typical of both diseases were observed in the same case earlier by Rossolimo.[9] In this respect, my case shows the greatest analogy to Jakob's,[10] his representing the chronic, mine the acute, stage. The tendency to wall formation, which could be observed in my case, was pronounced in the case of Waggoner and Löwenberg and was mentioned by Pette [11] in connection with diffuse sclerosis.

Some of the foci of my case correspond to the small perivenous changes seen in the type of demyelinating encephalomyelitis known as parainfectious or postvaccinal. From this point of view, analogies between my case and the subacute case published by Waggoner and Löwenberg, under the heading of concentric sclerosis, seem very important. Figure 1 of these authors, which shows small perivascular foci, a part of them poorly defined, bears great resemblance to my Figure 8. Pette also reported the presence in a case of diffuse sclerosis of small foci showing the character of parainfectious encephalitis.

Thus, analysis of the histopathologic findings in my case throws light on the formal genesis of the large demyelinated areas with typical features of Schilder's disease. It demonstrates their formation by fusion of perivascular foci of the type of both acute multiple sclerosis and perivenous encephalitis.

There is no diversity of opinion that Schilder's encephalitis is one of the processes which lead, at a later stage, to diffuse sclerosis. One of the main points in question is the discrimination of the inflammatory and the purely degenerative form of diffuse sclerosis. Mostly, the inflammatory changes are found in the more acute cases, whereas they are missing in the majority of cases with a delayed course. If there are exceptions in both groups, it should be borne in mind that most of the cases which are known in the literature had a course of at least several weeks. The really fulminant cases, such as that described here and those reported by Stewart, Greenfield, and Blandy, show definite inflammatory changes.

The formation of the demyelinated areas by small perivascular foci is not the privilege of the acute form. I have already quoted instances of subchronic or chronic lesions of this kind. Others could be added. In photomicrographs in the case of Davison and Schick,[12] with "complete" and patchy areas of demyelination, it can be recognized that the latter follow the direction of the vessels and that the extensive demyelination also shows patchy structure in its marginal parts.

8. Waggoner, R., and Löwenberg, K.: Konzentrische Sklerose, Arch. Psychiat. **101**:184, 1934.

9. Rossolimo, G.: Zur Frage über die multiple Sklerose und Gliose, Deutsche Ztschr. Nervenh. **11**:88, 1897.

10. Jakob, A.: Zur Pathologie der diffusen infiltrativen Encephalomyelitis in ihren Beziehungen zur diffusen und multiplen Sklerose, Ztschr. ges. Neurol. u. Psychiat. **27**:290, 1915.

11. Pette, H.: Die akut entzündlichen Erkrankungen des Nervensystems, Leipzig, Georg Thieme, 1942.

12. Davison, C., and Schick, W.: Encephalopathia Periaxialis Diffusa, Arch. Neurol. & Psychiat. **25**:1063, 1931.

Both the structural characteristics and the various intensities of the inflammatory changes are common in the diffuse demyelinating encephalitis of Schilder and the acute focal demyelinating encephalitides. As a further common feature, it is to be mentioned that both in the diffuse and in the focal demyelinating encephalitides the participation of hematogenous and adventitial cells, on the one hand, and of the microglia, on the other, may show great relative differences.

Pette [11] and Ferraro [12] advanced the theory that all forms of inflammatory demyelinating diseases, including perivenous encephalomyelitis and diffuse sclerosis, are the result of an allergic-hyperergic reaction. The main support of this theory is given in experiments which show that the consequences of parenteral extraneural injection of homologous or heterologous nerve tissue reveal a great similarity to, if not identity with, the lesions of perivenous encephalomyelitis in man (Kabat, Wolf, and Bezer [14]; Alvord and Stevenson [15]). Pette, extending the allergy theory to all inflammatory demyelinating diseases on the basis of clinical and histologic observations, spoke of "neuro-allergy."

In another paper,[16] I have pointed out that the variability of the inflammatory changes is compatible with the neuroallergic reaction. This variability is manifested in the relative intensity of the exudation, the emigration of hematogenous elements, and the microglial reaction.

The position of Schilder's disease among the processes which lead to diffuse sclerosis is thus based not on etiologic uniformity, but on the way in which the nervous system reacts, i. e., on the neuroallergic reaction. It is obvious that for eliciting this reaction exogenous factors are necessary. Yet the perivascular accentuation of the demyelination also occurs in the familial form of diffuse sclerosis. An example of this is the case of van Bogaert and Scholz.[17] The pathologic picture in this case differed in many points from that observed in Schilder's disease, as in the extent of the demyelination and in the cellular activity connected with myelin disintegration (accumulation of the products in large neuroglial elements in the case of van Bogaert and Scholz; microglial digestion in Schilder's disease). Marmoration of the affected areas can be detected in Figure 1 of Kaltenbach's [18] nonfamilial case of atypical disintegration. At any rate, one has to reckon with the possibility that also in some familial cases and in cases with atypical lipid disintegration a noxious agent escapes from the blood vessels. How far such a hypothesis is compatible with an endogenous etiology is beyond the scope of this study.

13. Ferraro, A.: Pathology of Demyelinating Diseases as an Allergic Reaction of the Brain, Arch. Neurol. & Psychiat. **52**:443, 1944.

14. Kabat, E. A.; Wolf, A., and Bezer, A. E.: Experimental Studies on Acute Disseminated Encephalomyelitis in Rhesus Monkeys, A. Res. Nerv. & Ment. Dis., Proc. **28**:113, 1950.

15. Alvord, E. C., and Stevenson, L. D.: Experimental Production of Encephalomyelitis in Guinea Pigs, A. Res. Nerv. & Ment. Dis., Proc. **28**:99, 1950.

16. Környey, S.: Die Entmarkungsencephalomyelitiden, Fortschr. Neurol., Psychiat. **20**:1, 1952.

17. van Bogaert, L., and Scholz, W.: Klinischer, genealogischer und pathologisch-anatomischer Beitrag zur Kenntnis der familiären diffusen Sklerose, Ztschr. ges. Neurol. u. Psychiat. **141**:510, 1932.

18. Kaltenbach, H.: Über einen eigenartigen Markprozess mit metachromatischen Abbauprodukten bei einem paralyseähnlichen Krankheitsbild, Ztschr. ges. Neurol. u. Psychiat. **75**:138, 1922.

In considering the relation of Schilder's disease to the other leucoencephalitides, one must take into consideration the fact that coalescence of the demyelinated foci and diffuse myelin rarefaction have often been observed in acute perivenous encephalitis. Later stages of measles encephalitis are known from the descriptions given by Walthard [19] and Malamud.[20] The confluence of the small foci to form large areas reminded Walthard of diffuse sclerosis. Malamud, however, considered only superficial the resemblance between the postmorbillous residuum and diffuse sclerosis. It must be admitted that in parainfectious encephalitis the rarefaction of the myelinated fibers is not so well outlined as in diffuse sclerosis, and that there is no sharp demarcation beneath the layer of the arcuate fibers. However, the extent and the demarcation of the large demyelinated areas of Malamud's Case 1 have their parallel in several cases interpreted in the literature as diffuse sclerosis, in which the process in some regions did not reach, and in others transgressed, the layer of the arcuate fibers, as, for example in Case 1 of Benoit.[21]

With respect to the common histopathologic features of the various leucoencephalomyelitides, it is easily understood that one meets diagnostic uncertainties or mistakes in the literature. As early as 1913, Krabbe [22] published the case of a 1-year-old child in which perivascular myelin destruction and glial proliferation were found. He interpreted these findings as the early stage of diffuse sclerosis. In the light of present knowledge there can hardly be any doubt that, in this case, one of the early descriptions of the parainfectious (perivenous) type of encephalitis was given by Krabbe.

The case of Hampel,[23] labeled as one of "sclerosing disease of the hemispherial white matter," deserves considerable interest. In this case (associated with Addison's disease, as in that of Siemerling and Creutzfeldt) several foci were observed in the white matter of the hemispheres, as well as in the pons and bulb. Some of these foci remind the author of multiple sclerosis and the glial seams of measles encephalomyelitis.

A case described as Schilder's disease by de Massary and Albeissar [24] is also worthy of attention. An agglomeration of small demyelinated foci was found, symmetrically located in the two hemispheres. Their perivascular arrangement could usually be recognized, and the white matter stained poorly in their neighborhood with the myelin methods. This pallor did not reach the subconvolutional fibers and was not sharply defined. Bertrand remarked that this finding showed greater resemblance to the type of postvaccinal encephalitis than to Schilder's disease.

19. Walthard, K. M.: Spätstadium einer "Encephalitis" nach Masern, Ztschr. ges. Neurol. u. Psychiat. **124**:176, 1930.

20. Malamud, N.: Sequelae of Postmeasles Encephalomyelitis, Arch. Neurol. & Psychiat. **41**:943, 1939.

21. Benoit, W.: Zur Frage der diffusen Sklerose, Ztschr. ges. Neurol. u. Psychiat. **140**:517, 1932.

22. Krabbe, K.: Beitrag zur Kenntnis der Frühstadien der diffusen Sklerose (die perivasculäre Marknekrose), Ztschr. ges. Neurol. u. Psychiat. **20**:108, 1913.

23. Hampel, E.: Morbus Addisonii und sklerosierende Erkrankung des Hemisphärenmarks, Deutsche Ztschr. Nervenh. **142**:186, 1937.

24. de Massary, J., and Albeissar, R.: Maladie de Schilder, Rev. neurol. **65**:100, 1936.

Wolf, Kabat, and Bezer [25] compared the demyelination of the monkey brain after intramuscular injection of brain tissue with that in a case of diffuse sclerosis, in which they considered the "diffuse area of demyelination consequent to the fusion of perivascular lesions." The relation of the two is the same as that of the coalescent lesions of parainfectious encephalitis to Schilder's disease. The analogies between the pathologic changes in the human brain and the experimental lesions caused by injections of nerve tissue, especially the variability of the histologic changes observed in both, justify the assumption that the same basic pathogenic mechanism is acting in the experimental and in the human inflammatory demyelinating diseases. This mechanism is the neuroallergic reaction. Incidental to this basic mechanism, additional factors decide whether perivascular demyelinating encephalitis assumes the features of diffuse sclerosis. The same may hold true for multiple sclerosis.

The confluence of the perivascular foci to form large demyelinated areas may be a matter of degree of the damage wrought by the causative agent. For such a fulminating process as that presented by the present case a single onslaught of maximal intensity must be assumed. In cases of gradual progression constituting perhaps the majority of all published cases of Schilder's disease, the assumption of a single onslaught seems less probable. In this connection the case of Jakob, in which the foci are stated to be of different ages, may again be mentioned.

SUMMARY

A case of rapidly fatal process is described in which histologic examination disclosed an extensive and fairly symmetrical inflammatory demyelination in the cerebral hemispheres. In each of the frontal lobes a large lesion was found, with a sharp demarcation characteristic of Schilder's encephalitis; in more posterior sections several large and small areas were detected, manifesting features of both Schilder's disease and the acute form of multiple sclerosis. Both myelin and cell preparations showed an accentuation of the process around small vessels. The small, partly independent foci were also perivascularly located. These findings support the assumption that large areas of demyelination typical of Schilder's disease develop by coalescence of small perivascular lesions. These lesions bear features partly of acute multiple sclerosis and partly of perivenous (parainfectious, etc.) encephalitis. The pathogenic mechanism underlying these different types of leucoencephalitis is the neuroallergic reaction. Unknown additional factors determine which type of leucoencephalitis develops.

25. Wolf, A.; Kabat, E. A., and Bezer, A. E.: Pathology of Acute Disseminated Encephalomyelitis Produced Experimentally in the Rhesus Monkey and Its Resemblance to Human Demyelinating Disease, J. Neuropath. & Exper. Neurol. **6**:333, 1947.

Society Transactions

BOSTON SOCIETY OF PSYCHIATRY AND NEUROLOGY

James L. Poppen, M.D., Presiding
Regular Meeting, Dec. 20, 1951

Use of Vitamin Therapy in Chronic Alcoholism. Dr. M. F. Trulson, Miss V. Heggie, Miss E. Sowles, Dr. R. Fleming, and Dr. F. J. Stare.

During the last few years Mardones, in Chili, and Williams, in Texas, have carried out experiments in which mice and rats are offered a choice of water or water plus 10% alcohol. They have found repeatedly that the choice may be influenced by the diet fed the animals and by the genetic strain. On this basis, Williams has formulated what he terms the genetotrophic theory of alcoholism. This has stimulated workers to investigate the genetotrophic aspects of alcoholism in man.

The present experiment, carried out at the alcoholic clinic of the Peter Bent Brigham Hospital, has consisted of placing patients on a regimen either of placebos or of high doses of vitamins to see whether the drinking patterns of these subjects may be influenced. Since October, 1950, 185 patients have been referred to the nutrition program; of these 100 have been followed for 6 to 15 months. The data on these 100 patients have been compiled under six categories: (1) lack of interest in program; (2) unsatisfactory response to therapy; (3) improvement, that is, reduction in drinking or change in pattern of drinking; (4) controlled drinking; (5) total abstinence; (6) concurrent use of medicaments with tetraethylthiuramdisulfide (antabuse®). The data provide some interesting observations: Improvement and controlled drinking were observed in 14 and 13% of the patients, respectively. With the exception of two patients, all in these two groups were receiving vitamin therapy. Patients in the other groups did not show any particular differences in response to placebo and the vitamin therapy. One of the main difficulties in the study was in determining whether or not the patients were taking the medicaments. Though the data are encouraging, it must be remembered that the patients must be observed for much longer periods and the data compared with those for other methods of therapy before one can draw conclusions as to the merits of vitamin therapy.

It should be emphasized that these studies with the use of large amounts of vitamins have no relation to the ordinary concept of deficiency disease, in the sense of scurvy or beriberi. They are formulated on the basis that the alcoholic has a metabolic aberration related to one or more of the enzyme or coenzyme systems involving the various vitamins. A considerable excess of the vitamins, far above the level that could be obtained with a good diet, may help to overcome this aberration. A good diet is important for the alcoholic, as for anyone else; but in this study extra quantities of vitamins, as pharmaceuticals, are given, in the idea of overcoming a possible metabolic error.

Hormone Treatment of Acute and Chronic Alcoholism and the Alcoholic Psychoses. Dr. Iver S. Ravin (by invitation) and Dr. Kermit Katz (by invitation).

Tetraethylthiuramdisulfide (Antabuse ®) Treatment of Chronic Alcoholism. Dr. Martha Brunner-Orne.

Nikethamide and oxygen should be at hand. In the experience of my colleagues and myself, the other medicaments proposed to counteract the tetraethylthiuramdisulfide-alcohol reaction have not proved efficient.

Trial tests are also helpful in determining the optimum amount of tetraethylthiuramdisulfide to be given as a maintenance dose. These "trials," or "whiskey tests," frequently have a psychological effect, but we have found that they are not essential. Many patients are not familiar with the tetraethylthiuramdisulfide reaction, and are not opposed to taking it, but do refuse to take the "trial" tests.

We believe that tetraethylthiuramdisulfide should always be given in conjunction with a complete rehabilitation plan, involving physical, emotional, and environmental aspects. The length of time during which the drug may be taken varies, from several weeks to years. During the period of adjustment to normal life its use is particularly valuable.

Many persons feel much better when they know they cannot drink. It helps them to resist the sudden urge to drink; apprehension and indefinite anxieties are substituted for by a real positive fear of the reaction to tetraethylthiuramdisulfide, a situation which they can handle better.

In many cases alcoholism is a symptomatic manifestation of an underlying emotional disturbance. It might well be that the sudden elimination of alcohol by means of tetraethylthiuramdisulfide therapy, without any other protective measures, may lead to the precipitation of psychotic manifestations in prepsychotic personalities. In some of the cases reported in which psychoses occurred after tetraethylthiuramdisulfide treatment, the question of *post hoc, ergo propter hoc* or *post hoc* is difficult to determine.

Tetraethylthiuramdisulfide was introduced in the therapy of alcoholism in 1948, and our own experience dates back to January, 1949; since then, we have treated about 300 patients. The drug is available as antabuse,® in tablets of ½ grain (0.037 gm.). When taken in combination with alcohol, it causes strong systemic reactions, flushing, nausea, vomiting, dyspnea, marked dropping of blood pressure, and sometimes collapse. These reactions are probably due to interference with the normal breakdown of alcohol, leading to an accumulation of acetaldehyde in the blood and tissues.

A thorough physical examination, including electrocardiography, blood cell count, and urinalysis, should always be performed before this medication is started. Cardiac or renal deficiencies are contraindications to the treatment.

Short periods of hospitalization are desirable and advantageous because many alcoholics are in physically run-down condition and improve much more quickly when hospitalized. Tetraethylthiuramdisulfide may produce discomfort during the initial period of administration. It is necessary to build up the drug level in the blood, which is then maintained by doses averaging from ½ to 1 tablet (0.037 to 0.065 gm.); occasionally only ¼ tablet (0.018 gm.) is given daily.

After the drug has been given several days, it is advisable in certain cases to make "trials," or "whisky tests." A small amount of whisky, from ½ to 1 fl. oz. (15 to 30 cc.) of 100-proof whisky is given, while the patient is carefully observed.

During the test period the patient is watched. Usually 5 or 10 minutes after the alcohol intake the reaction starts and lasts about one-half hour. Because of the sharp drop in diastolic blood pressure which may occur, it is advisable to keep the patient in bed during the trial.

We have observed a smaller percentage of psychotic manifestations than are usually reported in the literature. We use smaller doses of tetraethylthiuramdisulfide, which are reduced when even very mild side-effects appear.

It is advised that patients who take tetraethylthiuramdisulfide carry an identification card with them.

Statistical data are presented on the first 100 patients treated with tetraethylthiuramdisulfide, beginning January, 1949. We found that the results were better than those in a control group treated without the drug. This is the more significant in that we were then treating only patients for whom other methods had failed.

	Results				
	Very Good, %	Good, %	Fair, %	Poor, %	Unknown, %
Patients treated with antabuse®.....	22½	37	11¼	5	13
Patients treated without antabuse®.....	25	20½	33½	20	12½

In our opinion, tetraethylthiuramdisulfide has proved to be a valuable adjunct in the treatment of alcoholism, but it should be integrated with a complete rehabilitation program.

DISCUSSION ON PRECEDING PAPERS

DR. WILFRED BLOOMBERG: I should like to ask Dr. Stare what is known of the biochemistry of the genetic block of alcohol metabolism. Alcoholism is not a nutritional deficiency, but it sounds as though it were an alcohol deficiency, as though the alcohol released something that could not be used, because some genetic block prevented the development of an enzyme.

I realize the figures are preliminary, but I should like to raise a question about the controls. In this case, percentages have little interest to me unless expressed in terms of percentages of patients receiving placebo. Dr. Fleming said most of the contributions had come from physiologists, but all agree than one cannot ignore the psychiatric aspects. The taking in of something has meaning to the patient. I think that is part of the reason that an alcoholic can be cured by becoming a barbiturate addict. One cannot ignore the meaning to the patient of something ingested. It becomes of significance if comparison is made of vitamin- and placebo-treated patients.

DR. F. L. STARE: I must point out that we should not have been reporting on this study but for the request of Dr. Fleming. We are not yet at the stage of publishing our findings. I disagree with Dr. Bloomberg that alcohol is toxic. Such a statement must be qualified with the designation of the dose. Alcohol can be well metabolized; it provides 5 to 6 Cal. per gram. It is a chemical substance which the body can use. A specific enzyme, alcohol dehydrogenase, oxidizes it. I recall that two-thirds of our 175 patients received vitamins, and one-third, placebos. We should have preferred to have given alternate patients the vitamin or the placebo, but, for many reasons, that was not practical. The figures show that about 13 patients were seemingly controlled drinkers on vitamin therapy, and only 1 patient taking placebos could be so classified. There are, I believe, some 14% of the patients, in addition to those in the groups classified as total abstainers and controlled drinkers, who have shown improvement, in that alcohol is not as much a problem as before; the percentage showing improvement on placebo therapy is very much smaller.

Dr. Bloomberg asked about specific biochemical abnormalities. Perhaps a dozen specific biochemical abnormalities have been studied in molds and are known to be related to a specific gene. A certain mold can complete a specific chemical reaction; when the genetic structure of the mold is changed, this mold can no longer carry out the reaction. By increasing the vitamin that is specifically involved in these reactions, one can push the reaction to completion, thus overcoming the genetic block.

I know of no specific reactions involving the metabolism of alcohol that are definitely related to abnormal genetic structure. The only evidence is that whether certain strains of rats will drink water or water plus alcohol can be controlled by dietary factors. These rats show no evidence of any nutritional disease. That is one of the reasons that we say these studies should not be considered in the light of the usual deficiency diseases. Of course, nutritional deficiencies may exist in an alcoholic who has had insufficient food, has lost weight, or has been on a binge. We are thinking in terms of doses far in excess of these used for dietary supplements. For example, a man requires approximately 1 mg. of thiamine daily. We are giving the patients 30 mg. daily. Biochemically, there is a good theoretical reason to suspect that the genetotrophic theory which has been developed from studies with animals may have a human implication. Whether or not this can be proved only time will show.

DR. ELSE S. NEUSTADT, Quincy, Mass.: We have used adrenocortical extract and corticotropin at Hanover House for over a year in cases both of acute intoxication and of delirium tremens. From our experience, in acute intoxication, the results with adrenocortical extract are gratifying, in delirium tremens corticotropin gives excellent results. We have treated approximately 50 patients, most of them with acute intoxication.

My impression is that later we shall be able to make a better selection of patients in treating alcoholism with adrenocortical extract. Biochemists will probably be able to help us.

In a number of patients with delirium tremens the effects of corticotropin were striking. One patient, seemingly with delirium tremens, did not appear to respond to corticotropin. Later we learned that he had had a period of hallucinations of three to four weeks' duration; a diagnosis of alcoholic hallucinations was made.

We have used tetraethylthiuramdisulfide since 1949. This drug is most helpful in opening the way for psychotherapeutic treatment of alcoholic patients. There are certain patients who

are not able to maintain sobriety for any length of time and who may be reached by psychotherapy. In secondary alcoholism the anxiety cannot be treated properly before the patient has been sober long enough. Furthermore, tetraethylthiuramdisulfide is very helpful in treatment of patients who are under pressure situations, for instance, family situations, divorce actions, or court actions.

It is hard to give figures on therapeutic success, for even though a patient has repeated recurrences of drinking bouts, it does not mean that he cannot be helped; the whole situation and the general picture must be taken into consideration.

DR. F. L. STARE: One cannot expect any result if the patient does not take the medication. A fair number of patients who have not responded to use of vitamins have been transferred to tetraethylthiuramdisulfide therapy and have continued to show no benefit. Obviously, they were not taking the drug, and presumably not the vitamins.

DR. LEO ALEXANDER: Our statistical friends would take issue with the method of selecting controls.

DR. R. FLEMING: That point has been emphasized more than it should be. The patients one gets are unselected. Occasionally I see a young man in acute trouble with a court. He is a good subject for tetraethylthiuramdisulfide, and unless something is done right away he will be drinking again; one cannot experiment with such patients.

DR. M. F. TRULSON: We have patients from the same family, and the vitamin and the placebo do not taste alike. Such patients are suspicious. In the same family we have to give the same medication.

DR. SAMUEL W. JOEL: I should like to ask those who have had experience with the use of adrenocortical extract and corticotropin in the treatment of delirium tremens these questions: Is there any advantage in this therapy over the usually accepted methods? Does it have a better effect? Is it more rapid in its action? How about the disadvantage of the toxic effects of corticotropin? I am an adherent of the old-fashioned methods. I have not been discouraged by their results. Is there any real or practical value in the use of these newer drugs?

DR. MAURICE VICTOR: When one is passing judgment on the efficacy of any new treatment for alcoholism, it is important to keep clearly in mind the natural history of the illness and, in the case of the acute manifestations, the course of recovery with the more commonly used therapeutic measures.

My colleagues and I have interviewed and followed the clinical course of some 500 seriously afflicted alcoholic patients at the Boston City Hospital. In this group it was the rule, rather than the exception, to find a spontaneous period of abstinence of one to two years' duration. In some instances the period was considerably longer. The validity of any study that uses the length of the period of abstinence as a yardstick of therapeutic effect may be seriously questioned, unless it covers a large comparable group of alcoholic patients studied for a decade or longer.

We have had an opportunity to compare a large group of routinely treated patients with delirium tremens with a group who received corticotropin, in addition to sedation, hydration, and antibiotics. We observed no significant differences in the two groups, either in the mortality or in the rate of recovery.

The role of adrenal cortex extract in the treatment of alcoholic tremulousness is more difficult to judge. The difficulty is due largely to the wide individual variations in symptoms, which depend, in turn, on the patient's age and constitution, the amount and nature of what he drank, the state of his nutrition, the presence of other disease, and, significantly, the attitude of his doctors and nurses. It is our impression that the addition of hormone does not appreciably alter the tempo of recovery or the subsequent drinking habits.

Finally, a word of caution regarding the use of these drugs is in place. Given in large doses, they are capable of increasing the state of negative nitrogen balance, increasing potassium excretion, lowering resistance to infection, and exacerbating both tuberculous infections and peptic ulcers. All these side-effects are of prime importance in the alcoholic patient.

Because of their expense, serious side-effects, and lack of definite therapeutic effectiveness, we feel that the routine use of hormones in alcoholism is not yet indicated.

James L. Poppen, M.D., *Presiding*
Regular Meeting, Jan. 17, 1952

Value of Vertebral Angiography. Dr. Donald B. Freshwater.

A series of 50 patients who were subjected to percutaneous vertebral arteriography during 1950 and 1951 was reviewed in order to assay the difficulties of the procedure and its value to the patient. A simple technique was emphasized. The indications are (1) spontaneous subarachnoid hemorrhage, the cause of which is not shown by bilateral carotid angiography; (2) intracranial bruit, also of unknown origin, and (3) an atypical brain-stem or posterior-fossa syndrome, when diagnosis by air study fails.

The patients represent a successful 80% of all first attempts in use of the percutaneous procedure. Ten of the 50 patients had obvious vascular lesions. Of these, eight benefited directly from the procedure, four through surgical attack and four by avoidance of surgical exploration. Only one complication arose, and that was of a minor nature.

It is concluded that percutaneous vertebral angiography is an important diagnostic procedure prohibited neither by difficulty of performance nor by complications.

DISCUSSION

Dr. James L. Poppen: My colleagues and I have been impressed with the value of vertebral angiography. I should like to ask some of the men present to say something about their experience with the method. Except in unusual cases, we are not in favor of repeating arteriograms after the condition has been treated surgically.

Dr. D. Denny-Brown: The fusiform aneurysms of the basilar artery, as I have seen them, are the result of an atherosclerotic process in that vessel. It is that kind of atherosclerosis that I had understood reacted unfavorably to use of iodopyracet (diodrast®). The natural course of these aneurysms, besides causing damage to cranial nerves, is to produce effects by occlusion of the small vessels to the brain stem. Does not a pathological process of this kind, with narrowed openings to small lateral vessels, make use of iodopyracet inadvisable?

Dr. Joseph M. Foley: This technique and presentation call forth great admiration. I should like, however, to warn against the logical danger of interpreting a result as positive, i. e., as showing that a vessel is occluded, by a negative technique, i. e., the failure of the vessel to fill with dye. Two relevant anomalies occur in the vertebral-basilar system as one sees it in routine autopsy material. The vertebral artery on one side may be absent entirely, or it may be only a thin thread, in which situation the other vertebral artery is proportionally larger. Understandably, this alters the relation of the posterior inferior cerebellar arteries. Another relevant variation occurs when there is a very small posterior cerebral artery on one side. This is usually compensated for by a proportional increase in size of the homolateral posterior communicating artery, of which the posterior cerebral artery then appears to be a direct continuation. Thus, the occipital lobe may be getting its blood supply from the carotid system.

The occasions in which arteriography is necessary to the diagnosis of embolic or thrombotic occlusion of a cerebral vessel must be rare indeed. One would anticipate that these may be the situations in which arteriography may be attended with some risk to the patient.

Dr. James L. Poppen: Dr. Freshwater said he was very strict in determining whether or not there was a thrombus in the posterior cerebral artery by making carotid and vertebral arteriograms. Twenty-five per cent of the posterior cerebral arteries come off the internal carotid artery, as he will emphasize in his concluding comments. We perform bilateral arteriography to determine the adequacy of the collateral circulation.

Dr. Walter R. Wegner: I wish Dr. Freshwater would say more about his technique. The pictures were not very clear.

Dr. Julius Loman: I introduced the method of direct carotid angiography in 1935. At that time neurosurgeons were hesitant about using the closed method. Surgeons like to see everything exposed. Arteriography is really a neurological technique, and neurologists, if they have facility in puncture technique, should not hesitate to learn the method.

DR. JAMES L. POPPEN: I thought Dr. Loman showed Dr. Horrax and me his technique in 1934. I am not sure that I should agree with him that neurologists should learn arteriography, for the following through, not just the doing of the test, is important.

DR. DONALD B. FRESHWATER: I am in complete agreement with Dr. Denny-Brown that the fusiform, aneurysmal dilatations of the vertebral and basilar arteries which I have shown this evening are of atherosclerotic origin. I submit, however, that arteriography carries a slighter hazard than does cerebellar exploration, which was strongly indicated in each case. Vertebral arteriography with iodopyracet, or any other contrast medium, can be dangerous to the atherosclerotic patient as shown by the one death, which has been reported by others. This death was thought to be due to spasm of the basilar artery. I questioned the belief that any rigid, atheromatous vessel, particularly a cerebral one, could have the power of spasm. Dr. Denny-Brown's statement that the vascular plaques lead to the neurological deficits by their occlusion of branching vessels is an acceptable one. The added insult of even momentarily heightened ischemia of the brain stem from injection of iodopyracet may be fatal. On the other hand, the patients I am reporting had severe occipital headache, as well as neurological deficits. The success in treatment was simply in the relief of this pain, and perhaps in the reduction of the probability of future subarachnoid bleeding. There have been no serious difficulties in this admittedly small series of 50 vertebral arteriograms.

I appreciate Dr. Foley's reminding me of the many anatomical variations in the circle of Willis. It was my awareness of this variability that led to the establishment of the strict criteria for diagnosis of thrombosis by arteriography. I pointed out that the posterior cerebral artery demonstrated to be thrombosed by vertebral arteriography could not be filled by any route of injection, whereas the opposite posterior cerebral vessel filled very well and consistently by injection of the carotid artery on the same side and by injection of the vertebral artery from the opposite side. Likewise, on vertebral angiograms I have noted great disparity in the size of vertebral arteries in the presence of a basilar artery of normal caliber. I do not believe Dr. Foley meant to imply that the basilar arteries he has seen in this material were normal.

My answer to Dr. Wegner's request for more details on the technique of this procedure is to confess that I have no special tricks. There are points in the technique which can be made clear only by demonstration, and an invitation is extended to anyone interested.

Lobotomy Case Histories. DR. WALTER I. TUCKER.

Two case histories are presented to emphasize the notable results which can be accomplished in appropriate cases and to report the effects of the operation on the organic conditions (ulcerative colitis and anorexia nervosa) present.

CASE 1.—A single woman aged 31 had a history of recurrent ulcerative colitis for eight years, with seven hospitalizations for this disorder.

She had been under psychiatric care for 10 years, with intensive and prolonged psychotherapy and three courses of electric shock treatment.

Before operation, in May, 1951, she presented the picture of a severe obsessive-compulsive neurosis and had symptoms of subacute ulcerative colitis.

After bimedial prefrontal lobotomy she was relieved of all obsessive-compulsive symptoms, and by September, 1951, she was working, socially active, and relieved of all symptoms of colitis.

CASE 2.—A youth aged 18 had a three-year history of a severe obsessive-compulsive neurosis, manifested particularly by anorexia and preoccupation with bowel function. His weight had decreased from 160 to 81½ lb. (72.6 to 36.95 kg.); he presented evidence of pituitary depression and had severe anemia and leucopenia.

Forced feeding, administration of corticotropin, nonconvulsive electric stimulation, and psychotherapy had failed to effect any significant benefit.

In September, 1951, he had a bimedial prefrontal lobotomy, which resulted in complete relief of the obsessive-compulsive symptoms. In January, 1952, he weighed 181 lb. (82.1 kg.), and the blood count and endocrine functions showed no abnormality. He was active and unworried and was attending school.

Diagnostic Studies and Survival Statistics in a Series of Meningiomas of the Brain.

DR. GILBERT HORRAX.

Between 1933 and 1946 there were 168 meningiomas in a series of 1,146 verified brain tumors which my associates and I collected to the end of that period, representing 14.6% of our intracranial new growths. We have studied certain diagnostic criteria in the first consecutive 115 cases of these meningiomas, but our mortality and survival statistics cover the whole series of 168. Since we wished to have a follow-up period of five years or more, we chose 1946 as the final date covered by this study.

The chief symptom of which patients complained when they came under our care was headache (32.1%). This was the initial symptom only, and any or all of the symptoms may have been present with far greater frequency during the preoperative course. Convulsions, for instance, were present at some time prior to operation in 40.8% of patients. They occurred after operation in only 27.8%, including those who may have had only a single seizure. In one-half of all the patients convulsions after removal of the tumor have been controlled adequately by medication.

Other initial symptoms, which occurred infrequently, were unilateral weakness, loss of olfactory sense, ataxia, and difficulties with speech.

Roentgenograms of the skull gave reasonably accurate evidence of the type and situation of the growth in 47.8% of the patients. The protein content of the ventricular or spinal fluid was distinctly elevated in 68% of the 24 patients on whom such determinations were made.

It was believed that air studies, usually ventriculograms, were necessary in 56.5% of patients, either to make the diagnosis of tumor or to localize the growth with accuracy.

Mortality and Survival.—Twenty-three of the 168 patients died in the hospital after the operation, a mortality of 13.6%. However, during the last five-year period of this study there were only 5 deaths among 63 patients, a mortality of 7.9%.

Of the 145 patients who left the hospital, 114 (78%) survived from 5 to 18 years, and of these, 97 (85%) had either returned to some form of work or were in good health if not employed.

DISCUSSION

DR. JAMES C. WHITE: It might be of interest to discuss two points suggested by this excellent paper. Dr. Horrax did not say anything about tumors of this sort in children. At the Massachusetts General Hospital we have encountered three meningiomas in young patients between the ages of 5 and 13 years. All the patients died before the age of 30, from inexorable spread of their disease.

A 5-year-old boy was first operated on by another surgeon, who obtained an inadequate biopsy specimen of tissue blocking the posterior horn of the left ventricle. This was reported as astrocytoma. A postoperative hematoma developed, and the bone flap was removed. When I first saw him, three years later, a large hernia cerebri was developing, but the child was otherwise healthy. As time went on, he began to have Jacksonian seizures and loss of his right visual field, and the tumor became heavily calcified. Nevertheless, he continued to go to school until he was 15. On many occasions the family had been told that he probably had a benign tumor and that an exploration should be done, and they had also been so advised by Dr. Wilder Penfield. Only when he had deterioration from severe recurrent seizures was this agreed to. I then removed a meningioma weighing over 1,400 gm., 600 gm. of which filled the left posterior half of his skull. The patient died six months later, in status epilepticus. (This unusual case of the largest meningioma on record was reported in the *Journal of Neurosurgery* [**7**:455, 1950].)

A girl who had had her eye enucleated at the age of 7 years was followed from the time she was 20 until she died, at the age of 30. The specimen at the Massachusetts Eye and Ear Infirmary shows typical meningioma cells growing down the optic nerve and producing detachment of the retina. As increasing tumor tissue recurred in the orbit, displacing her glass eye, Dr. V. Kazanjian and I removed the muscle cone and infiltrating tumor locally. Up to 1940 she had evidence only of a thin meningioma en plaque in the orbital plate, which could not be dealt with on account of the total enucleation of her orbital contents. While I was away during the war, signs of cerebellar ataxia developed, and she died after pneumoencephalography. Permission for autopsy was not obtained, but Dr. W. J. Mixter was of the opinion that the tumor had extended caudalward along the brain stem as far as the pons.

The third case was that of a boy whose mother had been operated on by Dr. Cushing and Dr. Horrax and who died with multiple meningiomas. The boy had had a lateral dislocation of his left eye at the age of 13. Transfrontal exploration did not reveal any intracranial involvement. A biopsy specimen of the tumor was taken through the orbital roof, and later the tumor was resected from its attachment to the medial wall by a frontal approach. A form of meningiomatosis developed, and before the patient died, in 1949, at the age of 22, I had removed or visualized nine separate similar tumors.

You may be interested in mortality results from a general clinic, where not only the visiting staff, but also the residents, do these operations. About one-fifth of our meningiomas have been removed by the residents. We have tried to select cases and help them with difficulties. I have divided the statistics on 148 cases into two series. During the five years before the War the case mortality rate was higher—21%, or 13% when calculated for the total number of operations. In the last five years our over-all case mortality was 11.6% (7.9% for the total number of operations). For the senior members of the visiting staff the case mortality has been 9.2%. I am convinced that one can safely teach residents to do tumor surgery if one grades their proficiency, starts them gradually, and is ready to help them at any moment of emergency. Just as long as the mortality statistics can be kept within the justifiable range, I am sure it is better for the community as a whole to have these young men learn their major operative technique by personal, firsthand experience under direct supervision while in resident training than to acquire it after they have set up on their own outside.

Dr. Paul Jossmann, Belmont, Mass.: Incontinence of urine in cases of meningioma was found in cases in which the tumor originated from the falx and the motor centers for bladder control were involved bilaterally. I should like to ask Dr. Horrax whether his observations confirm the concept of this working mechanism. Incontinence may be a diagnostic aid in meningiomas if present in association with other findings which suggest new growth in the vicinity of the falx.

Dr. Gilbert Horrax: I do not recall just how young these patients were. We have had two under 12 years of age. I suppose most young children go to Children's Hospital. I remember a child under 10 at Peter Bent Brigham Hospital. One sees incontinence in many cases of brain tumor, not of meningioma only. At the moment we have a woman who had a meningioma of the falx, and she has been incontinent since operation, although conscious. Incontinence may be present irrespective of whether or not the tumor comes from the falx. Some large frontal tumors may produce incontinence. In all our meningioma series either I or Dr. Poppen, or the two of us together, did the operation. Some of the younger members of the neurosurgical staff have also operated in a few cases. We have not been able to turn the work over to the younger men, for we feel that it is our responsibility.

Aneurysm of the Anterior Cerebral Artery: Surgical Aspect. Dr. James L. Poppen.

Abstracts from Current Literature

EDITED BY DR. BERNARD J. ALPERS

Physiology and Biochemistry

INFLUENCE OF LOW-FAT DIET ON BLOOD LIPID LEVELS IN HEALTH AND IN MULTIPLE SCLEROSIS. V. A. WILMOT and R. L. SWANK, Am. J. M. Sc. **223**:25, 1952.

Wilmot and Swank, following up the epidemiologic studies of Swank which suggested a relation between incidence of multiple sclerosis and amount of dietary fat intake, made a study of the blood lipides in patients with multiple sclerosis while on their usual diets and for long periods on diets containing 20 to 50% of the fat normally consumed.

Fifteen patients and presumably healthy controls were studied for total phospholipide, free total cholesterol, and total fatty acids. No essential differences were found between normal subjects and patients with multiple sclerosis with respect either to lipide levels or to the response of lipide levels to the change in diet.

FOLEY, Boston.

CEREBRAL PHYSIOLOGY OF THE AGED. J. F. FAZEKAS, R. W. ALMAN, and A. N. BESSMAN, Am. J. M. Sc. **223**:245, 1952.

Cerebral hemodynamics and oxygen consumption were investigated in asymptomatic persons 50 years of age or older, in patients with cerebrovascular lesions, and in patients with cerebrovascular disease with psychosis. The average elderly person had increased cerebrovascular resistance and decreased blood flow as compared with members of a younger group. These changes were more marked in elderly people with clinical evidence of cerebrovascular disease. The cerebral oxygen consumption of elderly people, regardless of their symptoms, was less than that of the younger subjects. Administration of 10% oxygen did not alter the oxygen consumption. Inhalation of 5% carbon dioxide increased the cerebral blood flow and cerebral oxygen consumption.

BERLIN, New York.

RHOMBENCEPHALIC CONVULSIVE ACTIVITY. J. W. MARKHAM, K. M. BROWNE, J. C. JOHNSON, and A. E. WALKER, Bull. Johns Hopkins Hosp. **89**:442, 1951.

The intravenous administration in the cat of strychnine in doses of 0.018 to 0.022 mg. per kilogram of body weight is followed by the appearance of large rhythmical waves in the electrical tracing taken from the exposed cerebellar surfaces. These waves are roughly sinusoidal, with a frequency of 10 to 30 cps and voltages which are relatively constant for a given preparation but vary from 100 to 400 μv. in different experiments under similar conditions. Some of the characteristics of this phenomenon have been studied in greater detail in the present study.

The authors describe an unusual type of electrical activity in the electrorhombencephalogram of the cat and the monkey. This is characterized by regular rhythmical waves of high amplitudes (20 to 450 μv.) at frequencies of 10 to 32 cps, lasting from several minutes to one hour. Activity of this type was observed after topical, intravenous, or local injection of strychnine; intravenous injection of methyl-*bis*- or methyl-*tris*-(B-chloroethyl) amine (nitrogen mustard) and of chlorophenothane U. S. P., and electrical stimulation of the cerebellum. Wave forms of this type were recorded from the cerebellar cortex, dentate nuclei, brain stem, and spinal cord.

The physiological mechanisms which may be responsible for this phenomenon are discussed. The possibility of a reticular internuncial system common to the cerebellum, brain stem, and spinal cord as the basis for this type of activity is suggested.

The characteristics of the normal electrocerebellogram of the cat are given, as well as the effects of pentylene tetrazole, picrotoxin, caffeine, nikethamide, physostigmine, acetylcholine, pentobarbital, mephenesin, procaine, penicillin, and streptomycin, administered locally, intravenously, or topically.

ALPERS, Philadelphia.

STRUCTURE OF THE NUCLEOLUS AS REVEALED BY THE ELECTRON MICROSCOPE. E. BORYSKO and F. B. BANG, Bull. Johns Hopkins Hosp. **89**:468, 1951.

The high magnification attained by the electron microscope made it possible for the authors to observe complex structure within the nucleoli of a number of normal and pathological tissues. They found that, in addition to homogeneous, structureless nucleoli, nucleoli possessing a characteristic filamentous structure were observed in sections of 11 normal and pathological tissues. No evidence of a nucleolar membrane was found in any of the preparations.

The occurrrence of nucleolar structure in the wide variety of vertebrate cells and tissues examined suggests that, with a few exceptions, it may be expected to be found in all vertebrate cells. The fact that it was observed in normal as well as pathological tissues indicates that it is a normal morphological feature of the cells. The simultaneous presence, in similar cells of a tissue, of homogeneous nucleoli and nucleoli with filamentous structure, as well as the occasional appearance of nucleoli which combine both features, suggest to the authors that a transformation from a homogeneous mass to a complex filamentous tangle, or the reverse, may occur within the nucleolus in the course of its functional cycle.

ALPERS, Philadelphia.

INFLUENCE OF DIETARY PYRIDOXINE ON GLUTAMIC DECARBOXYLASE ACTIVITY OF BRAIN. E. ROBERTS, F. YOUNGER and S. Frankel, J. Biol. Chem. **191**:277, 1951.

Alpha-aminobutyric acid is present in the free form in large amounts in brain, where it is formed from glutamic acid by a *l*-glutamic acid decarboxylase. The enzyme requires pyridoxal phosphate as coenzyme, which can be synthesized in brain from adenosinetriphosphate and pyridoxal. This decarboxylase has a high degree of substrate and coenzyme specificity. A manometric method for the assay of the glutamic acid decarboxylase activity of brain is described. The values obtained in the presence of excess pyridoxal phosphate gave an estimate of the total quantity of apoenzyme, while those obtained in the absence of added coenzyme allowed an estimate of the relative degree of saturation of apoenzyme with coenzyme. The glutamic acid decarboxylase activity of brains of rats maintained on the experimental diet with a pyridoxine-containing supplement of the B vitamins for a prolonged period was closely similar to that found in animals fed the stock diet. When pyridoxine was omitted from the vitamin supplement, there was a decrease of approximately 50% in the degree of saturation of the apoenzyme with coenzyme, but the content of apoenzyme was normal. Refeeding pyridoxine to rats previously made deficient resulted in a return of the activity to a normal level. The feeding of excess pyridoxine to animals on the stock diet did not result in an increase in activity. From results obtained with rats which were given desoxypyridoxine, while being fed a deficient diet, it does not seem likely that the acceleration of the deficiency symptoms by the antagonist is related to an increased rate of depletion of the glutamic acid decarboxylase activity of brain.

PAGE, Cleveland.

CHOLINE ACETYLASE: VI. SUBSTITUTION OF ADENOSINETRIPHOSPHATE ACETATE BY THIOLACETATE. D. NACHMANSOHN, I. B. WILSON, S. R. KOREY and R. BERMAN, J. Biol. Chem. **195**:25, 1952.

An enzyme which in the presence of adenosinetriphosphate forms acetyl coenzyme has been prepared from pigeon liver extracts by fractional ammonium sulfate precipitation. The term acetylkinase is proposed for the enzyme. The highest activity was found in the fraction between 30 and 37% ammonium sulfate. Both choline and sulfanilamide are acetylated when adenosinetriphosphate acetate is replaced in the full system by thiolacetate. The latter compound acts in the choline-acetylating system prepared from brain, as well as with Escherichia coli extracts, but in extracts of squid head ganglia thiolacetate was unable to replace adenosinetriphosphate acetate. Dialyzed liver extract catalyzes the acetylation of cysteine and mercaptoethanol by thiolacetate. No coenzyme is required in these reactions. In compounds in which the SH group was replaced by other groups, such as serine, ethanolamine (2-aminoethanol), glycol, and glycylglycine (glycylaminoacetic acid) no acetylation occurred. Acetylation of mercaptoethanol was also obtained with adenosinetriphosphate acetate. In this case coenzyme is required.

PAGE, Cleveland.

ETHYL(3-HYDROXYISOAMYL)BARBITURIC ACID AS THE PRINCIPAL METABOLITE OF AMYTAL. E. W. MAYNERT, J. Biol. Chem. **195**:397, 1952.

A metabolite of amobarbital (amytal®) isolated from the urine of dogs was identified as 5-ethyl-5-(3-hydroxyisoamyl)-barbituric acid. The compound was synthesized by the addition of water to 5-ethyl-5-(3-methyl-2-butenyl)-barbituric acid and by the oxidation of amobarbital with chromic acid. Isotope-dilution experiments in dogs demonstrated that after an anesthetic dose of labeled amobarbital 67% of the excreted isotope was present as this alcoholic end-product.

PAGE, Cleveland.

OXIDATION OF ENDOGENOUS FATTY ACIDS OF RAT TISSUES IN VITRO. M. E. VOLK, R. H. MILLINGTON and S. WEINHOUSE, J. Biol. Chem. **195**:493, 1952.

Radioactive, carboxyl-labeled palmitate was administered intragastrically to rats fasted 24 hours, and at various intervals thereafter tissues were removed, sliced, or minced and allowed to respire in vitro. All tissues, including brain and skeletal muscle, were found to oxidize the labeled acid. At short intervals after the feeding of the labeled acid, the respiratory carbon dioxide had a higher specific activity than the total fatty acids of the same tissue, indicating the presence of a metabolically active fatty-acid fraction which is not in rapid equilibrium with the tissue lipides. This metabolically active fraction was not identifiable with phospholipide, and phospholipides do not appear to be obligatory intermediates in the transport of fatty acids into cells.

PAGE, Cleveland.

A MITOCHONDRIAL PREPARATION FROM MAMMALIAN BRAIN. T. M. BRODY and J. A. BAIN, J. Biol. Chem. **195**:685, 1952.

The present studies clearly show that mitochondria play a prominent role in oxidative and phosphorylative processes in brain, just as they do in other tissues. It remains for future studies to elucidate the manner in which the energy so gained is converted into the unique function of nerve tissue, i. e., transmission. The preparation of a particulate preparation from brain having the properties of mitochondria is described. Such a preparation oxidizes at high rates the majority of the Krebs citric-acid-cycle intermediates and glutamate. With proper supplementation it is possible to demonstrate associated phosphate uptake with P : O ratios of from 2.5 : 3.0. Under the conditions employed, the preparation does not oxidize at appreciable rates alanine, aspartate, or octanoate (caprylate), nor does it exhibit any glycolytic activity.

PAGE, Cleveland.

EFFECTS OF X-IRRADIATION IN NEWBORN RATS. S. P. STEARNER and E. J. B. CHRISTIAN, J. Exper. Zool. **118**:495 (Dec.) 1951.

Newborn rats were exposed to x-rays shortly after birth (one-half to five hours) or at 1 or 2 days of age, with radiation doses ranging from 400 to 1,000 r and exposure rates of 6,40, and 80 r per minute.

Of the youngest rats 100% died within two weeks after exposure to any dose, and the mean survival time decreased with increasing dose. Approximately 50% of deaths occurred within four days after exposure to 600 r at a rate of 80 r per minute, but the deaths were delayed in the groups exposed at the rate of 6 r per minute. No effect of variation in dosage rate was observed after exposure to 400 and 800 r. However, exposure to 1,000 r produced a shorter mean survival time when delivered at 6 r per minute than when delivered at the higher rate. The effects of dosage rate upon survival two and four days after irradiation were shown to be significantly different for doses of 600 and for doses of 1,000 r.

While resistance to x-rays increased rapidly during the first two days after birth, no effect of variation in dosage rate upon survival was observed at any dose level tested.

Generalized edema, hyperemia, and renal hemorrhages were prominent autopsy findings at one to two days after irradiation in animals exposed within five hours after birth. The gross changes which occurred later were typical of those that accompany acute radiation deaths. In addition, multiple cerebral hemorrhages developed within one day after irradiation.

Cerebellar and medullary hemorrhages appeared after five to seven days, while those in the cerebrum decreased in size and number. The transparent cranial roof permitted direct observation of brain lesions in the living animals. The relation of the autopsy findings to the early deaths is discussed, especially the predilection of the hemorrhages for renal and central nerve tissue.

REID, New Brunswick, N. J.

EFFECTS OF ADENINE COMPOUNDS ON ELECTROCORTICAL ACTIVITY. F. ROBINSON, and R. A. HUGHES, J. Neurophysiol. **14**:387, 1951.

Observations on 25 cats were carried out to study the pharmacologic effects of the adenine series, so that further information concerning their effects upon spontaneous and pharmacologically induced electrocortical activity might be obtained.

It was found that optimal doses of the various adenine derivatives on intravenous administration produced transient or, less frequently, persistent obliteration of the acetylcholine spike potentials without alteration of concurrent strychnine-induced spikes or depression of the control electrocortical activity. Similarly, selective inhibition of acetylcholine-induced spikes was noted with intravenous administration of atropine sulfate.

Topical application of the adenine compounds to the cortex inhibited acetylcholine spike potentials but did not affect the control electrocorticogram or the strychnine spikes. A definite order of ascending potency of the adenine series was noted in regard to this selective inhibitory action; adenine was the least effective, and adenosinetriphosphate was the most effective, with adenosine, adenosine-3-monophosphate, adenosine-5-monophosphate, and adenosinediphosphate exerting an intermediate effect.

The mechanism whereby the adenine nucleotides inhibit electrical discharges due to acetylcholine, and not strychnine, is not clear from their studies; but Robinson and Hughes believe that their results cast doubt on the theory that considers acetylcholine as the universal central synaptic transmitter. It is usually regarded that acetylcholine exists in the tissues in an inactive form, linked to certain tissue constituents, and that it is not susceptible to enzymatic destruction by cholinesterase; when released, it is physiologically active and is rapidly destroyed by cholinestrase. The adenine nucleotides may exert their effect by causing a shift in this dynamic equilibrium and in this way reducing the chemical stimulus for synchronous neuronal firing.

The authors discuss the possibility that acetylcholine and strychnine may act upon different cortical neuronal groups, i. e., cholinergic and noncholinergic.

ALPERS, Philadelphia.

THE NUCLEUS CERVICALIS LATERALIS: A SPINOCEREBELLAR RELAY NUCLEUS. B. REXED, and A. BRODAL, J. Neurophysiol. **14**:399, 1951.

A hitherto neglected nucleus is described in the cat. It is situated as a longitudinal cell column in the lateral funiculus of the first and second cervical segments of the spinal cord, ventrolateral to the dorsal horn. Its cells resemble those of the column of Clarke. The authors suggest that this nucleus be called the "nucleus cervicalis lateralis."

Experimental studies demonstrate that this lateral cervical nucleus sends its fibers to the cerebellum and that it receives afferent fibers from lower levels of the cord. Rexed and Brodal point out that this new spinocerebellar pathway is but one of many systems subserving the transmission of spinal impulses to the cerebellum.

ALPERS, Philadelphia.

CORTICAL REPRESENTATION OF VISCERAL AFFERENTS. V. E. AMASSIAN, J. Neurophysiol. **14**:433, 1951.

While the pattern of cortical response to tactile stimulation of the body surface has been extensively investigated, little is known of the central representation of visceral sensibility. In the hope of demonstrating a cortical representation of visceral pain, a study was made of the central projection of the afferent fibers distributed with the sympathetic outflow to the viscera because they provided the major sources of the information which leads to the sensations of visceral sensation and pain. The technique consisted of applying mechanical or electrical stimuli to visceral structures and recording the resultant electrical changes at different levels of the central nervous system.

The author found that electrical stimulation of afferent neurons distributed with the sympathetic outflow to the viscera gives rise to primary cortical responses, which are maximal in the trunk region of contralateral sensory Areas I or II of the rabbit, cat, dog, and monkey. An ipsilateral splanchnic representation in Area II of the cat was demonstrated.

The primary cortical response and localized secondary repetitive waves were obtained with strengths of splanchnic stimulation too weak for reflex movement. The second and third early waves and the generalized secondary cortical responses were obtained with strengths of stimulation causing reflex movement. Only the third early wave is secondary to the reflex movement. Recovery of excitability in the splanchnic and somatic afferent projection systems is similar.

ALPERS, Philadelphia.

COLLATERAL AFFERENT EXCITATION OF RETICULAR FORMATION OF BRAIN STEM. T. E. STARZL, C. W. TAYLOR, and H. W. MAGOUN, J. Neurophysiol. **14**:479, 1951.

The distribution of afferent collaterals to the reticular formation of the brain stem was investigated in the cat by probing for potential changes evoked by somatic and auditory stimulation.

In the case of each modality, a rich supply of collateral connections to the midbrain tegmentum, subthalamus, hypothalamus, and ventromedial thalamus was encountered. These findings offer an explanation for a number of the generalized consequences of afferent stimulation which have been difficult to understand in terms of conduction within classic sensory paths. Specifically, they indicate that the arousing and awakening influences of sensory stimulation may be exerted directly and at a subcortical level, by collateral excitation of the reticular activating system in the brain stem.

ALPERS, Philadelphia.

THREE CEREBRAL CORTICAL SYSTEMS AFFECTING AUTONOMIC FUNCTION. P. D. WALL, and G. D. DAVIS, J. Neurophysiol. **14**:507 (Nov.) 1951.

Fifty-five rhesus monkeys and two chimpanzees were used in a comparative study of the areas of cortex which produce blood-pressure changes on stimulation. Lesions and stimulations were made by a stereotaxic machine. Precautions were taken to remove peripheral sensory fibers from the surface of the cortex. Pronounced blood pressure changes followed stimulation of the following areas: sensorimotor cortex, anterior cingulate gyrus, posterior orbital surface, anterior portion of insula, and anterior temporal lobe.

The response of the sensorimotor cortex was shown to be independent of motor movement, epileptic discharge, the premotor area, and the hypothalamus. Isolated section of the pyramid completely abolished the responses.

The posterior orbital surface and the anterior portion of the insula were shown to be almost identical in their effects on blood pressure. Destruction of the hypothalamus was shown to abolish the blood pressure response from these areas but did not influence the respiratory response, which may depend on the caudate nucleus.

The temporal lobe was shown to have a very strong influence on blood pressure by a pathway which did not pass through the hypothalamus. The anterior cingulate gyrus may affect blood pressure by a mechanism dependent on the temporal lobe.

Wall and Davis conclude that two large and highly effective areas in the cortex can influence blood pressure by mechanisms which do not involve the hypothalamus.

ALPERS, Philadelphia.

EXPERIMENTAL APPLICATION OF ULTRASONICS TO THE LOCALIZATION OF BRAIN TUMORS: PRELIMINARY REPORT. L. A. FRENCH, J. J. WILD, and D. B. NEAL, J. Neurosurg. **8**:198 (March) 1951.

This report concerns an experimental attempt to apply ultrasonic pulses to the localization of brain tumors. The purpose of these experiments was to examine the possibility of locating, at the time of operation, subcortical neoplasms without the use of brain needles. The experiments were based on the principle that high-frequency sound waves, when driven through tissues, are believed to travel at a rate proportional to the tissue density and to the tissue

elasticity. These sound waves are reflected by surfaces involving change in density or elasticity, known as interfaces, and echoes are produced. The time interval before reception of the echo varies according to the texture and thickness of the tissue which the waves traverse. With these known data, it was postulated that when ultrasonic pulses were sent through normal brain tissue the presence of an underlying subcortical neoplasm might be ascertained by measuring this time interval.

It was found that when pulsed ultrasonic vibrations were sent through normal and neoplastic cerebral tissues the texture of the neoplastic cerebral tissue was such that the ultrasonic response was approximately twice that of normal cerebral tissue. Subcortical cerebral neoplasms were located in autopsy material by this method of investigation.

Pulsed ultrasonic vibrations of this frequency did not produce demonstrable damage in the cerebral hemispheres of experimental animals.

ALPERS, Philadelphia.

PROCAINE BLOCK OF FRONTAL LOBE WHITE FIBERS AS A MEANS OF PREDICTING THE EFFECT OF PREFRONTAL LOBOTOMY: I. EXPERIMENTAL STUDIES. O. BAILEY, W. T. SMALL, and F. D. INGRAHAM, J. Neurosurg. **9**:21, 1952.

This paper concerns itself with the study of efforts to predict, in some measure at least, the outcome of the treatment of mental disorders by physical means, such as the division of the white fibers in the frontal lobes of the brain.

Procaine hydrochloride in 2% solution was injected into the frontal white fibers of cats and a few monkeys. The color reaction which demonstrated the procaine in tissue is described. As judged by this reaction, local diffusion of procaine solutions in the frontal white matter is minimal and disappears in less than one hour.

Histologic evidence of residual damage was slight; tissue changes were no greater than those caused by the injection of the same amount of isotonic sodium chloride solution.

Escape of the procaine solution into the subarachnoid space and the ventricular system is a most serious complication but can be avoided by controlled technique.

So far as could be ascertained in these animal experiments, the procedure was regarded as safe for use in human patients.

ALPERS, Philadelphia.

EFFECT OF CORTISONE ON GROWTH OF TRANSPLANTED EPENDYMOMAS IN MICE. R. J. BRZUSTOWICZ, H. J. SVIEN, W. A. BENNETT, and G. M. HIGGINS, Proc. Staff Meet., Mayo Clin. **26**:121 (March 28) 1951.

The tumor used in this study was an ependymoma produced by the implantation of methylcholanthrene into the brain of a C_3H mouse. The inhibiting effect of cortisone on the growth of subcutaneously transplanted ependymomas of the myxopapillary type was studied in five series of C_3H male mice. With doses of the hormone larger than 0.5 mg. daily, serious toxic effects were induced in the animals, as well as striking inhibition of tumor growth. A daily dose of 0.5 mg. ordinarily did not produce toxic effects but did incite definite inhibition in the growth of the tumor, as indicated by a decrease in its size and weight. Total inhibition or complete regression of tumor growth did not occur. Histologically, the tumors of animals given 0.5 mg. of cortisone daily showed large areas of necrosis and degeneration, whereas tumors of equivalent age in control animals showed little or no change.

ALPERS, Philadelphia.

A STUDY OF THE HYPERGLYCAEMIC FACTOR IN THE URINE OF PSYCHOTICS. J. W. WALKER and W. MAYER-GROSS, Brit. J. Exper. Path. **32**:51 (April) 1951.

Walker and Mayer-Gross, studying the hyperglycemic factor of Meduna and Vaichulis in psychotic patients, were puzzled by the observation that the rise in blood glucose seemed to be due to at least two agents. Their technique was similar to that used by Meduna, involving adsorption and elution of the urine and injection of the fractions into the peritoneal cavity of rabbits. Study of the effects of the separate fractions indicated that there were actually two hyperglycemic agents. The first fraction was weaker and quicker-acting and was shown to consist of the salts of uric acid. The second fraction, stronger and slower-acting, was found

associated with the amino-acid content of the extract. This supposition of a protein component is consistent with the suggestion that the second hyperglycemic agent is hormonal.

FOLEY, Boston.

EFFECT OF ADRENALINE [EPINEPHRINE] ON SECRETION OF CORTICAL HORMONE IN THE HYPOPHYSECTOMIZED DOG. MARY PICKFORD and MARTHE VOGT, J. Physiol. **112**:133 (Jan.) 1951.

In the intact animal infusion of epinephrine causes an increase in the output of adrenocortical hormones, which can be detected by an increase in the survival time of rats given arterial blood from the animal receiving the injection. In hypophysectomized dogs, injection of epinephrine caused no increase in output of adrenocortical hormones provided the hypophysectomy was complete. Traces of anterior lobe were sufficient to produce a detectable response to epinephrine. Treatment of the hypophysectomized dogs with corticotropin did not alter the response except that after infusion of epinephrine the blood of the treated animals shortened the survival time of adrenalectomized rats. The nature of this response was not determined. It was noted that corticotropin alone increased the output of adrenocortical hormone in the hypophysectomized dog.

It was concluded that epinephrine increases the output of adrenocortical hormones through an increase in secretion of corticotropin, but that it also acts on the adrenal cortex by some other means.

THOMAS, Philadelphia.

VIBRATION AND HEARING. L. HALPERN, Confinia neurol. **10**:386, 1950.

Halpern offers the hypothesis that the sense of vibration must be looked on as a function supporting the sense of hearing. Three cases are cited for the development of the argument. Case 1 is that of a girl deafened by meningitis who was able to perceive at a distance up to 4 meters the tap of a reflex hammer on the floor. Case 2 is that of a man with diabetic pseudotabes who could perceive no tapping on the floor when hearing was artificially blocked. Case 3 is that of a woman who had total deafness of the right side with a total loss of vibration in the right side of her body. Halpern argues: "These circumstances led me to suppose that the loss of hearing was *connected* with the homolateral loss of vibration and that the acoustic apparatus would have functioned normally if the necessary stimuli could have reached it. The homolateral loss of vibration affected also the perceiving ear and obstructed not only the stimuli of vibration but also those of sound." He concludes that disturbed hearing is not necessarily based on affected acoustic function.

FOLEY, Boston.

Neuropathology

PRODUCTION OF EXPERIMENTAL ENCEPHALOMYELITIS WITH CALCIUM ACETATE COMPOUND EXTRACTED FROM BRAIN TISSUE. A. FERRARO and L. ROIZIN, J. Neuropath. & Exper. Neurol. **10**:395, 1951.

A total of 25 guinea pigs, divided into two groups, were used for the induction of experimental allergic encephalomyelitis with calcium acetate compounds extracted from the brain tissue.

Histologic studies disclosed circumscribed or diffuse (to a less extent) inflammatory reactions involving the meninges and the parenchyma at various levels of the central nervous system. The inflammatory exudate was more frequently perivascular and consisted of both hematogenous and histogenous elements, the percentage of which varied in relation to different stages of the inflammatory process. Frequently plasma cells appeared mixed with the various elements of the exudate. The process of demyelination was rather light and mostly perivascular.

Both the clinical and the neuropathologic findings were essentially similar to those previously reported in allergic encephalomyelitis in which the whole brain plus Freund's adjuvants was used as antigen.

The authors believe that it is still too early to attribute specific antigenic properties to the various lipid or protein fractions of the brain. However, there is indication that some of the chemical components of the brain, when used separately, possess antigenic properties capable of

inducing an encephalomyelitic process. Of these, the calcium acetate fraction, which is predominantly a protein compound, appears as the most potent one.

ALPERS, Philadelphia.

A CASE OF ATYPICAL ENCEPHALOMYELITIS RELATED TO ACUTE PERIVENOUS ENCEPHALOMYELITIS. J. RADERMACHER, Rev. neurol. **80**:742, 1948.

In a man, 15 days after an illness diagnosed as "grippe," acute ascending paralysis developed, with death in four days from bulbar involvement. Clinically, despite the long incubation period, the diagnosis was acute poliomyelitis.

Histologic examination revealed an inflammatory process primarily of the white matter, involving predominantly the cord and medulla but affecting also the brain stem, optic radiations, centrum ovale, and cortex. In the contiguous gray matter the neural elements were mostly intact. The anterior horns, bulbar nuclei, locus niger, and cortex showed rare cellular alterations. In all cases the major involvement was of the white substance, where the reactive process was most sharply localized around small and medium veins, with gradual diffusion into the parenchyma and, to a slighter degree, along the surface of the neuraxis.

The lesions themselves consisted of intra-adventitial collars of lymphocytes, surrounded by more diffuse microglial cuffs, constituting in each case a small granuloma. Demyelination was present but slight. Lesions were less marked in the roots and minimal in the spinal ganglia and peripheral nerves. There was widespread engorgement.

The lesions were less strictly perivenous and marginal than in typical postvaccinal encephalomyelitis studied at its height. Perhaps the longer survival period (if one accepts the grippal illness as the invasion) explains the differences in this case, namely, a less purely microglial perivascular reaction, diffusion of the reaction, and beginning appearance of a microglial response.

The case as a whole cannot be identified with any typical form of Landry's paralysis, and it is with perivenous and acute parainfectious encephalitis that the condition is most clearly related. That this kind of response can appear in the absence of any exanthematous or postvaccinal disease seems of sufficient importance to be reported.

Meninges and Blood Vessels

MENINGITIS DUE TO LISTERIA MONOCYTOGENES. F. G. LINE and W. B. CHERRY, J. A. M. A. **148**:366, 1952.

Two cases of meningitis due to Listeria monocytogenes in newborn infants are reported. The first patient died at the age of 13 days, 24 hours after readmission to the hospital, despite treatment with penicillin, sulfadiazine, and dihydrostreptomycin. The second patient, whose illness started when she was 6 days old, recovered when aureomycin and penicillin were used as the principal treatment. This patient was treated initially with a multiplicity of drugs, but she showed no improvement clinically or bacteriologically until after sensitivity tests were reported, showing aureomycin to be the drug of choice, and this medication was started. Several months later obstructive hydrocephalus developed, and a Tonkelson operation was performed. Pulmonary complications developed after operation, and she died at the age of 9 months.

The authors describe L. monocytogenes as a Gram-positive bacillus which has been isolated from patients who have infectious mononucleosis. It has not been proved that this organism is the causative agent of infectious mononucleosis. It has been isolated from animals, but the part played by animals as a reservoir of infection for human beings is not known.

Although the epidemiology of the disease is not known, it is significant that these two infants were born in the same delivery room within two days, that the family of the baby who died lived on a farm and was in contact with farm animals, that the mothers shared a common bathroom, and that the infants were in the hospital nursery together for 24 hours.

ALPERS, Philadelphia.

PRIMARY CEREBRAL THROMBOPHLEBITIS. J. C. SMITH, J. A. M. A. **148**:613, 1952.

Thrombophlebitis may be primary or secondary. The primary form is of unknown cause and is often termed recurrent thrombophlebitis, or migratory thrombophlebitis. The vessels affected are principally the superficial veins of the upper and lower extremities, although involvement of the visceral vein is not uncommon.

In some instances primary thrombophlebitis precedes or accompanies the development of thromboangiitis obliterans. It is not established that in all or most cases primary recurrent or migratory thrombophlebitis is associated with thromboangiitis obliterans. Primary thrombophlebitis of cerebral veins occurs in the absence of intracranial arterial disease.

The clinical and pathologic features of such a case are described in a patient who had signs suggestive of thromboangiitis obliterans of the lower extremities. Examination of the cerebral vessels and brain revealed only recent thrombosis and acute inflammation of the veins. However, the clinical manifestations during the six years before death suggested that the thrombophlebitis was probably recurrent. The cerebral arteries were normal except for slight arteriosclerosis. Lesions of extracranial vessels were found only in the left coronary and right common iliac arteries. Although autopsy revealed no arterial changes consistent with thromboangiitis obliterans, the clinical diagnosis was suggested in the patient by the occasional pain in the calves on exertion, the dusky-red discoloration of the dependent feet, the blanching of the feet on elevation, and the absence of a palpable dorsalis pedis pulse in both feet.

ALPERS, Philadelphia.

SPONTANEOUS SUBARACHNOID HEMORRHAGE IN INTRADURAL TUMORS OF THE LUMBAR SAC: A CLINICAL SYNDROME. E. F. FINCHER, J. Neurosurg. **8**:576, 1951.

With present-day attention centered on the "ruptured intervertebral disk" in accounting for lumbago-sciatica handicaps, and with the enthusiasm for cerebral angiography in cases of spontaneous subarachnoid hemorrhage, the author calls attention to a possible syndrome associated with certain lumbar intradural tumors.

The study is based on five cases. From a detailed study of these five cases of tumors of the cauda equina associated with spinal-subarachnoid hemorrhages, it seems clear that the symptoms of these growths in their early development are entirely subjective. There is no intimation in the beginning of this disease of any motor, sensory, or sphincteric dysfunction of the spinal cord.

The diagnosis should be suspected on the appearance of one or more bouts of intractable pain in the lower extremity and accompanying profound cephalalgia. The development of spontaneous subarachnoid bleeding in these patients, as disclosed on spinal puncture, should indicate the diagnosis. The finding of bloody spinal fluid should prompt early myelographic contrast studies, before compressive or destructive spinal-nerve-root symptoms are in objective evidence.

ALPERS, Philadelphia.

DIAGNOSTIC VALUE OF CAROTID ARTERIOGRAPHY IN TWO ATYPICAL CASES OF SUBDURAL HEMATOMA. P. WERTHEIMER, J. LECUIRE, A. LEVY, and J. RIISHEDE, Revue oto-neuro-oftal. **23**:499, 1951.

The authors report two cases in which carotid arteriography was a distinct help in diagnosis of subdural hematoma. The first patient, a man aged 31, was admitted because of increasing intracranial pressure and complete third-nerve paralysis. There was no history of accident. The onset of the illness had begun three months previously with headaches on exposure to the sun. The headaches were in the right frontoparietal area and were accompanied by nausea and vomiting. Change of behavior and mental clouding soon appeared, with slow pulse, ptosis of the right lid, and a Babinski sign on the left. Papilledema was observed in the right eye. On admission, there were stiffness of the neck, complete paralysis of the right third nerve, bilateral papilledema, mild hemiparesis on the left, and a bilateral Babinski sign. An electroencephalogram showed a right frontal focus. A carotid arteriogram revealed a right-sided subdural hematoma. This was treated, with complete recovery.

The second patient, a man aged 65, was admitted in coma after headache of three weeks' duration and progressive clouding of consciousness. In 1947 he was in a serious traffic accident; he suffered no loss of consciousness but had mild transitory confusion. He had no post-traumatic headache. Later in the same year severe hypertension appeared, with mild nitrogen retention. The present illness began with left-sided headaches, which became more frequent and more intense. In two weeks mild hypersomnia appeared. This progressed to torpidity, clouding, and, finally, coma. On his admission to the hospital, neurologic examination showed hyperreflexia on the right side and a bilateral Babinski sign. The fundi presented thin vessels but no papil-

ledema. The blood urea was 75 mg., and the sugar 102 mg., per 100 cc. The bleeding and clotting times were normal. An electroencephalogram was normal. A carotid arteriogram showed a subdural hematoma in the right frontoparietal region. The patient made a complete postoperative recovery.

The authors emphasize the value of carotid arteriography in the diagnosis of subdural hematoma. Pneumoencephalography merely shows the presence of a space-occupying lesion. There are some cases in which a diagnosis is made practically on the basis of the findings in carotid arteriography alone.

N. SAVITSKY, New York.

Diseases of the Brain

TRAUMATIC ENCEPHALOCELES OF THE ORBIT. A. B. KING, A. M. A. Arch. Ophth. **46**:49, 1951.

King reports two cases of traumatic encephalocele of the orbit, occurring probably through congenital defects in the roof of the orbit. In rare cases the floor of the anterior fossa may be fractured, making a path for prolapse of the intracranial contents.

The first case cited was that of a patient in whom a prolapse of the frontal lobe of the brain developed after exenteration of the orbit for a malignant tumor. Intracranial removal had been attempted previously, but the defect in the orbital roof had not been repaired. The second case illustrates the formation of an encephalocele after extensive trauma to the dura and floor of the anterior fossa of the skull. Protrusion of the globe was noted several months after the accident. In the first instance death occurred from the basic neoplasm. In the second instance the child made an uneventful recovery.

SPAETH, Philadelphia.

CEREBROSPINAL RHINORRHEA FROM CRANIOMASTOID FISTULA. R. H. AMES, W. D. FARMER, and W. H. MILLS, A. M. A. Arch. Otolaryng. **53**:451, 1951.

Leakage of cerebrospinal fluid from the nose is by no means a rare sequel of head trauma. Such a finding is generally regarded as pathognomonic of a communication in the region of the paranasal sinuses or the cribriform plate. It has been shown, however, that in rare instances rhinorrhea may result from a communication between the subarachnoid space and the mastoid or middle ear, the fluid passing through the Eustachian tube and into the nasopharynx.

The authors report such a case of cerebrospinal fluid rhinorrhea resulting from a traumatic craniomastoid fistula in a child of 6 years. Preoperative identification of the site of leakage by catheterization of the Eustachian tube enabled the correct surgical approach to be made and prevented a misdirected exploration of the anterior fossa.

ALPERS, Philadelphia.

METASTATIC HYPERNEPHROMA OF THE BRAIN FROM A NEUROSURGICAL POINT OF VIEW. T. P. STÖRTEBECKER, J. Neurosurg. **8**:185, 1951.

A series of 19 cases of metastatic hypernephroma (carcinoma of the kidney), occurring among a total of over 3,000 cases of brain tumor, is presented. The frequency of hypernephroma among the metastatic brain tumors is about 13%. Metastasis to the brain appears in most cases to be solitary.

Patients can live for several years after extirpation of metastatic hypernephroma of the brain; in one case the patient is still alive 14 years after the operation on the brain. The prognosis appears to be most favorable in those cases in which the primary tumor in the body has been diagnosed earlier and removed, e. g., by nephrectomy, before symptoms manifesting cerebral metastasis appear.

ALPERS, Philadelphia.

INTRANASAL ENCEPHALOCELE. W. P. WILLIAMSON and P. A. BARELLI, J. Neurosurg. **8**:231, 1951.

Encephalocele, or congenital protrusion of the brain or meninges through the skull, is not uncommon. The most frequent site of such a lesion is occipital. In a series of 84 reported encephaloceles, 63 were occipital, 9 parietal, 6 frontal, 5 nasal, and 1 presenting through a defect in the cribriform plate into the nasopharynx.

The authors report two cases of intranasal encephalocele with relief of rhinorrhea by intracranial approach. In the first case, the broad nose, the history of two attempts at removal of a nasal polyp, and the long history of rhinorrhea in the absence of head trauma made the diagnosis obvious. In the second case, since there was a history of a linear skull fracture two years before, the surgeon assumed that the rhinorrhea was simply traumatic and had not anticipated the true nature of the lesion until its actual exposure at operation. The skull fracture had undoubtedly torn the base of the encephalocele to precipitate the initial onset of the spinal-fluid leakage.

Williamson and Barelli point out that intranasal encephalocele is probably commoner than is generally believed and that it should be considered in the differential diagnosis of nasal polyp and rhinorrhea.

ALPERS, Philadelphia.

ASTROCYTOMA GRADE III ASSOCIATED WITH PROFUSE SUBARACHNOID BLEEDING AS ITS FIRST MANIFESTATION. R. L. DESAUSSURE JR., C. D. SCHEIBERT, and L. A. HAZOURI, J. Neurosurg. **8**:236, 1951.

Many reports in the literature suggest that cerebral neoplasms may cause subarachnoid bleeding, usually minimal in amount. A few cases of profuse subarachnoid hemorrhage due to malignant brain tumor have recently been reported. The case reported here is unique in that the history was brief and cerebral neoplasm was not suspected.

A man aged 27 was seen in stupor 36 hours after slight trauma. The history and examination and laboratory findings were consistent with subarachnoid bleeding associated with leaking cerebral aneurysm. A cerebral tumor on the right was not suspected. The patient was considered to have an aneurysm, since it has been shown that in the majority of cases profuse subarachnoid bleeding is caused by aneurysm.

Study of the left carotid angiogram demonstrated a vascular anomaly in the area, but the type of anomaly was not identified. It was thought best to rule out a tumor in this area by air studies. The spinal fluid at this time was clear and colorless and within the normal pressure range. Pneumoencephalography was performed, revealing an unsuspected tumor of the right frontal lobe. This tumor surrounded the anterior horn of the right lateral ventricle and is believed to have been responsible for the subarachnoid bleeding because of its location and vascularity.

The tumor in this case (astrocytoma, Grade III) was partially removed and the tip of the right frontal lobe amputated. The patient made an uncomplicated recovery and was given a course of deep x-ray therapy. Neurological findings two months after onset of symptoms were essentially normal, and the patient had returned to his previous occupation.

The authors suggest from a study of this case that air studies should be included as part of the diagnostic study of patients with subarachnoid bleeding in whom an aneurysm cannot be demonstrated.

ALPERS, Philadelphia.

ELECTROENCEPHALOGRAPHIC EVIDENCE OF THALAMIC AND HYPOTHALAMIC EPILEPSY. E. L. GIBBS and F. A. GIBBS, Neurology **1**:136, 1951.

A search was made for 14- and 6-per-second positive spikes in the electroencephalograms recorded during sleep of 300 control subjects. This pattern was found in eight cases (2%). In a group of 5,000 patients with epilepsy or suspected of having epilepsy, 14- and 6-per-second positive spikes were encountered in 312 cases, or 6%. Such spikes are distorted forms of the normal sleep patterns which have been shown in animals to originate in the thalamus and hypothalamus. The diffuseness of the discharge and the general positivity of the spikes suggest a subcortical origin.

The clinical correlates of 14- and 6-per-second positive spike discharges suggest epileptic disorder in the thalamus and hypothalamus; attacks of pain, rage, and vegetative symptoms are common. As compared with other types of epileptic and epileptiform disorders, 14- and 6-per-second positive spikes are relatively benign. A few discharges of this pattern, particularly in children, in the absence of symptoms should not be regarded too seriously. They are likely to remain asymptomatic, discharges disappearing with increasing age. When symptoms are

present, demonstration of such disorder is important not only as an aid to diagnosis, but as a clue to treatment. Such disorder usually responds well to a combination of diphenylhydantoin (dilantin®) and phenobarbital, or diphenylhydantoin and methylphenylethylhydantoin (mesantoin®).

ALPERS, Philadelphia.

GLIOMAS INVOLVING THE SPLENIUM OF THE CORPUS CALLOSUM. B. SCHLESINGER, Neurology **1**:419, 1951.

The series of 20 neoplasms verified at autopsy which form the basis of this report includes not only lesions of the splenium and forceps major, but also gliomas which cross the midline in the region of the posterior portion of the corpus callosum. The present study was undertaken in the hope that symptoms due to involvement of splenium might be distinguished from distant and neighboring effects by a comparison of the various clinical manifestations and a correlation of clinical and surgical experiences.

The survey revealed that gliomas of the splenium of the corpus callosum develop mostly in persons past middle age and frequently produce profound disturbances in memory in the inaugural phases of the disease, prior to the onset of intracranial hypertension.

Mental changes were present in 100% of cases; sensorimotor signs, in 85%; intracranial hypertension, in 70%; temporoparieto-occipital signs, in 50%; brain stem signs, in 45%; cerebellar signs, in 45%, and basal ganglia signs, in 35%. The frequent occurrences of cerebellar and midbrain signs, which were apt to be associated, is probably due to both direct and indirect pressure effects in the region of the tentorial notch.

The gliomas under consideration, most of which belong to the spongioblastoma multiforme group, are apt to produce seepage of blood into the subarachnoid fluid spaces and irritation of the meninges, with resulting xanthochromia, pleocytosis, and increase in total protein. Cerebrospinal fluid abnormalities were present in the nine cases in which a spinal puncture was performed. Owing to the absence of neurologic abnormalities in the early stages, and the distant effects of the neoplasm in the advanced stages, of the disease, its clinical diagnosis is difficult. The cerebrospinal fluid findings, therefore, gain added importance.

The author attempts to account for the presence and different types of mental changes in tumors of the splenium, the midportion, and the genu of the corpus callosum.

ALPERS, Philadelphia.

IRON ENCEPHALOPATHY. C. A. BIRCH and M. TILL, Brit. M. J. **1**:62 (Jan. 13) 1951.

Birch and Till describe the case of a woman aged 54 in whom the intravenous administration of 380 mg. of iron over a period of nine days was followed by the development of severe cerebral manifestations, which they tentatively attributed to iron encephalopathy. They point out that the intravenous administration of certain recognized proprietary preparations of iron have proved valuable and are comparatively nontoxic in controlled dosage but that the use of unproved preparations can be dangerous.

ECHOLS, New Orleans.

SOLAR HEADACHE. G. MURPHY, Prensa méd. argent. **41**:2665, 1951.

Murphy reports in detail three cases in which headache appeared on exposure to the sun. Headache usually appears in the summer months in out-of-door workers and is usually most pronounced in the middle of the day and the early afternoon. It is severer during clear weather and usually disappears when the patient goes indoors. It is usually frontal in location, and sometimes retro-ocular and pulsatile during the height of the attack. It is sometimes accompanied by photophobia and conjunctival injection. Severer attacks are accompanied by nausea, vomiting, and photopsias. Febrile episodes are usual; sweating of the face and forehead is not infrequent. Weakness is sometimes observed during exacerbation of cephalalgia. Epinephrine and ergotamine cause the headache to disappear, confirming its probable vascular nature. The headache is apparently not a reaction to increased temperature, but in some way is a response to the solar rays. Glare is an accessory etiologic factor. The patients were treated with vitamin A, antihistaminics, and dehistaminization, with success.

N. SAVITSKY, New York.

Diseases of the Spinal Cord

PROGRESSIVE SPINAL CORD DISEASE: SYNDROMES ASSOCIATED WITH HERNIATION OF CERVICAL INTERVERTEBRAL DISKS. K. J. STRULLY, S. W. GROSS, J. SCHWARTZMAN, and T. J. C. VON STORCH, J. A. M. A. **146**:10, 1951.

The purpose of this report is to reemphasize the necessity for the early recognition and treatment of surgically amenable lesions causing compression of the cervical portion of the spinal cord. This compression may result in syndromes closely resembling certain progressive diseases affecting the spinal cord, such as multiple sclerosis, combined system disease, amyotrophic lateral sclerosis, and syringomyelia. Careful examination, however, will reveal each such syndrome to be atypical in some significant respect.

Strully and his colleagues studied six cases of surgical lesions simulating various degenerative diseases. The diagnosis of "degenerative cord disease" (one case), syringomyelia (one case), multiple sclerosis (two cases), amyotrophic lateral sclerosis (one case), and combined system disease (one case) had discouraged any active therapy. In all cases, however, the syndrome was slightly atypical. In all, the symptoms were insidious in onset and the course was unusually prolonged (in one case, 16 years). In all cases the signs and symptoms could readily be accounted for by lesions below the foramen magnum. In four cases the total protein of the spinal fluid was increased. In five there were osteoarthritic lipping and a narrow intervertebral space at the level of the lesion. In five myelographic examinations of the cervical region of the spinal cord revealed a moderate or minimal defect at the level of the lesion. In all six cases the pathologic process was a calcified, herniated intervertebral disk, associated with osteoarthritic lipping in such fashion as to produce definite compression and angulation of the cord.

Because of the nature of the lesions, surgical intervention was, in all but one case, limited to freeing the cord by section of the dentate ligaments. While it is too early to report the final result of operation in these cases, some improvement has already been evidenced in four patients, from three to seven months after operation.

ALPERS, Philadelphia.

SECOND ATTACKS OF POLIOMYELITIS: REPORT OF A CASE WITH AUTOPSY FINDINGS. A. L. HOYNE and I. LIPTON, J. A. M. A. **146**:707, 1951.

Hoyne and Lipton report a second, and fatal, attack of poliomyelitis in a woman aged 31, with autopsy findings. As a consequence of the first attack, five years previously, the patient had severe weakness of the left lower extremity with moderate atrophy. As expected, at autopsy there was evidence of a past pathologic process, consisting of moderate atrophy of the left anterior horn in the lumbar portion of the cord, and microscopic examination revealed extensive destruction of the nerve cells.

The second attack terminated in death due to respiratory failure four days after the onset of symptoms.

Microscopic examination of the cerebral cortex showed intense congestion of the overlying meninges. The central ganglia showed marked engorgement throughout. There was a large focal extravasation of blood near the left lateral ventricle. About this area was pronounced diffuse infiltration of round cells and leucocytes, and many of the ganglion cells had disappeared or exhibited moderate neuronophagia. Most of the vessels were surrounded by round cells. The dentate nuclei of the cerebellum showed slight engorgement. The ganglion cells appeared intact. There was slight diffuse infiltration of round cells and leucocytes. A few vessels had small collars of round cells. The pons and medulla were conspicuously engorged. Most of the ganglion cells appeared intact. Throughout the tissue there were moderate diffuse infiltration of round cells and a few focal collections of leucocytes. Most of the vessels were surrounded by collars of round cells. There was pronounced congestion of the entire spinal cord and meninges. The cervical and thoracic portions of the cord were notable for the disappearance of most of the ganglion cells from the anterior horns. The gray matter exhibited marked diffuse infiltration of round cells and leucocytes, and the white matter also showed slight infiltration. Most of the vessels of the gray matter and some of the vessels of the white matter were surrounded by collars of round cells and leucocytes. Changes in the lumbar portion of the cord were more accentuated, especially on the left side. A few foamy cells were present in the anterior horns. An absence of ganglion cells was noted on the left side. The few remaining ganglion cells on

the right side exhibited pronounced satellitosis and neuronophagia, and a few showed myelination. Collections of round cells were prominent about the posterior roots.

The authors suggest that second attacks of poliomyelitis are due to an immunologically different strain against which the patient has no previous immunity.

ALPERS, Philadelphia.

SPINAL TUMORS DIAGNOSED DURING THE FIRST YEAR OF LIFE, WITH REPORT OF A CASE. W. H. MOSBERG JR., J. Neurosurg. **8**:220, 1951.

The author was able to find in the literature only 23 instances in which an intraspinal tumor had been diagnosed during the first year of life. The predominant tumor in this group was the lipoma, which occurred in 6 of the 23 cases. Four cases of dermoid, 4 of teratoid, 3 of teratoma, 3 of sarcoma, and 1 each of neurofibroma, neuroblastoma, and intramedullary glioma made up the remainder of the series. In one-half the cases the diagnosis had been made before death, and in 11 cases the tumor had been attacked surgically. It is of interest to note the high incidence of associated anomalies in this group.

To the above series the author adds a case, that of a 5-month-old child who became paraplegic within a period of four weeks. The symptoms were relieved by laminectomy and partial removal of an extradural thoracolumbar leukemic deposit. The patient was subsequently found to have lymphatic leukemia.

At the time of the last examination, 65 days after operation, the patient showed no signs of neurologic disorder.

ALPERS, Philadelphia.

OBSERVATIONS ON THE 1950 POLIOMYELITIS EPIDEMIC IN ISRAEL. W. FOLK, Harefuah **21**:7, 1951.

During 1951, 1,600 cases of poliomyelitis were seen in Israel. The height of the epidemic was in June. Only 1% of the patients were Arabs. The disease was severest in adults who had immigrated from the Netherlands and the United States. Most of the patients were from the North; 60% were males; 93% were 5 years of age or under; 56% were 2 years of age or under, and 30, or 7.4%, were reported to be below 6 months of age. Nineteen were 5 months of age or less. One case was that of an infant 17 days old whose mother had the disease at the same time. No difference of susceptibility was observed between infants who were breast fed and those who were artificially fed. There was no difference between children who were well nourished and those with malnutrition. No instances of a second attack were reported. Only two sibling pairs were affected in this series. In three cases the infection apparently took place while the child was in the hospital. No case of paralysis appeared in a limb which had recently been vaccinated. Eighty-seven patients had no paralysis. Prodromal symptoms, usually lasting two or three days, were noted in two-thirds of the cases. Paralysis was found twice as frequently in the lower limbs as in the upper limbs. The deltoid was the muscle most frequently involved in the upper limbs. In the lower limbs the muscles involved most frequently were the tibialis anterior, the peroneus, and the quadriceps. In 22 cases the only manifestation of poliomyelitis was facial paralysis. In 34 cases facial paralysis was present with bulbar or spinal paralysis. No changes were found in the electrocardiogram in any of the cases, although autopsy revealed myocardial involvement. In 9% of the cases the spinal fluid contained less than 10 cells per cubic millimeter; in 40%, 20 to 100 cells; in 1%, over 1,000 cells. The largest number of cells was 2,515 per cubic millimeter. The total protein of the spinal fluid was higher in cases of severe paralysis. The blood cell count was normal in all cases. In 10 to 15% of the patients admitted with the diagnosis of poliomyelitis, some other disease simulating it was found. Of 51 deaths, 26, or 13.2%, occurred in the first 24 hours. The greatest mortality was in infants. Forty-two of the patients had to be put in respirators; 67% of these died. The mortality in the cases of bulbar involvement was 67%. The author notes that quarantine did not seem to diminish the number of cases or protect persons from contracting the disease. None of the medical or nursing personnel became ill with poliomyelitis. The author noted his disappointment with the use of drugs for reduction of spasms. He prefers the application of heat. He warns against the use of tubes in patients who cannot swallow. He prefers prolonged intravenous feedings, avoiding in this way the danger of vomiting and aspiration. Tracheotomy was performed in eight patients, three of whom recovered.

N. SAVITSKY, New York.

Peripheral and Cranial Nerves

MECHANISM INVOLVED IN POLYNEURITIS AS EXEMPLIFIED BY POST-DIPHTHERITIC POLYNEURITIS. M. R. BROWN, Ann. Int. Med. **36**:786, 1952.

Because the cause of postdiphtheritic polyneuritis is known, Brown made a survey of 53 affected patients in an effort to understand the mechanism involved in 40 patients with a polyneuritis of unknown origin but similar to the postdiphtheritic type in its clinical manifestations, spinal-fluid changes, and autopsy findings.

Postdiphtheritic polyneuritis in these 53 patients was remarkably consistent in its course. There was weakness of the palate about 10 days after the acute infection. About four to five weeks later the patient experienced numbness and tingling of the arms and legs, and the deep reflexes were lost. Seven to eight days after these symptoms, peripheral sensory loss and weakness of the extremities, and even of the trunk muscles, followed. At the same time, other cranial-nerve paralyses developed in about two-thirds of the patients. The nerves to the eye muscles were particularly susceptible to the diphtheria toxin.

The spinal fluid exhibited the Guillain-Barré syndrome of an increase in protein without an increase in cell count.

The clinical and spinal fluid findings in these 53 patients with postdiphtheritic paralysis were compared with those in the 40 patients with polyneuritis of unknown origin. Of these 40 patients, 13 had had an infectious disease; 12 had diabetes; 1 had dermatomyositis, and 2 had received injections of animal proteins.

Brown believes it is likely that an allergic response of the nerve cell to a foreign substance is involved in both the polyneuritis due to diphtheria toxin and that of unknown cause. In that case, if used early in the course of the disease, corticotropin or cortisone should be effective in both diseases.

ALPERS, Philadelphia.

PSYCHOSOMATIC ASPECTS OF MÉNIÈRE'S DISEASE. E. P. FOWLER and A. ZECKEL, J. A. M. A. **148**:1265, 1952.

Fowler and Zeckel suggest that a basic disorder of personality usually is present in patients suffering from Ménière's disease and that the first attack and many subsequent attacks are caused by vascular phenomena in the labyrinth which are brought on by emotional stimuli, so that Ménière's disease is primarily a psychosomatic disorder.

Twenty-three patients with clear-cut Ménière's disease were studied. Each patient was subjected to a battery of personality studies. The ages ranged from 24 to 60, and 13 patients were men. The majority of them were of an aggressive appearance and temperament. Most were unusually rugged. The 10 women were less uniform in type, but, like the men, tended to be extroverts.

Fowler and Zeckel found a relationship between the appearance of the conjunctival circulation and changes within the otic mechanisms in cases of Ménière's disease during the intravenous injection of procaine. Procaine administered intravenously was selected for therapeutic trial in Ménière's disease because it breaks up lumping and increases the speed of circulation of small blood vessels in cats with experimentally produced sludge. Since intravenous administration of procaine, simultaneously with the disappearance of sludge, also altered or stopped the tinnitus in several cases of Ménière's disease, the authors present this as evidence for a vascular theory of the cause of the disease.

To substantiate further their contention that sludging may cause Ménière's disease, they observed the conjunctival vessels before and after experimental psychic stimulation. They found that the effect of the psychogenic factors seems to involve slowing and arrest of circulation in the small blood vessels within the labyrinth on an adrenergic pattern. Excessive lumping of red blood cells and early blood sludge in the bulbar conjunctiva can be seen before and after attacks. They suggest that these lumps of blood, when caught in the smaller vessels of the labyrinth, are instrumental in the production of the labyrinthine hydrops which has been found to be the characteristic pathologic feature of the disease.

The authors conclude that in cases of advanced Ménière's disease a large percentage of patients will require psychotherapy in addition to medical or surgical help. In early cases psychotherapy may reverse the course of the disease, so that there are few, if any, residuals.

They also believe, since there is much similarity in the significant traits of all affected patients, that group psychotherapy should be considered, especially in clinics where individual treatment is too time-consuming and costly.

ALPERS, Philadelphia.

Treatment, Neurosurgery

IMPORTANCE OF REST IN THE TREATMENT OF EARLY CONVALESCENT POLIOMYELITIS. W. GREEN, A. M. A. Am. J. Dis. Child. **83**:4, 1952.

This paper, based upon personal daily supervision of over 200 patients in the early convalescent stage of poliomyelitis during a recent epidemic, is presented by the author to minimize the value of any specific form of active therapy and to emphasize the importance of the role of rest. The experience gained in supervising the treatment in this large number of cases convinced him that increasing the activity of the patient in the early convalescent stage of poliomyelitis and permitting him to ambulate never succeeded in hastening the return of muscle power, but frequently retarded it and led to harmful substitution.

When to increase the activities of a patient in the early convalescent stage of poliomyelitis and when to allow ambulation depend upon fine judgment, and no categorical time limit can be set. The effects of increased activity and ambulation must be carefully appraised by frequent muscle examination and observation of gait.

ALPERS, Philadelphia.

BILATERAL TRANSVERSE OPTIC NEURITIS: REPORT OF TWO CASES WITH CORTISONE THERAPY. V. L. SMITH, A. M. A. Arch. Ophth. **46**:363, 1951.

Smith reports two cases of sudden binocular blindness, each occurring in an apparently healthy patient without obvious reason. Cortisone was administered in each case, and visual improvement was rapid. This improvement may have been coincidental, but it justifies the use of cortisone in similar cases.

SPAETH, Philadelphia.

SYMPTOMS AND TREATMENT OF PITUITARY TUMORS. O. HIRSCH, A. M. A. Arch. Otolaryng. **55**:268, 1952.

In this review article, Hirsch classifies pituitary tumors from the surgical point of view. Basic symptoms for the diagnosis of pituitary tumors are enumerated.

The achievements and limitations of x-ray and operative treatment are briefly discussed, and Hirsch describes his transsphenoidal-septal method and the treatment of solid and cystic tumors by this method. He emphasizes the value of additional radium treatment to prevent regrowth and to destroy or shrink the remnants of the tumor not radically removed.

The operative mortality in the transsphenoidal-septal method is now 5% (including craniopharyngiomas) and is decreasing with the aid of antibiotics. The author presents the immediate results in single cases of each group of intrasellar, craniosellar, and cystic tumors and reviews a series of 277 cases with follow-up periods for 4 to 19 years. Nineteen cases are mentioned in which the improvement has been maintained for 19½ to 30 years. He believes that the transsphenoidal method should be considered with regard to the low risk and long-lasting cures in cases of pituitary tumors with enlarged sella, whenever operative treatment is indicated.

ALPERS, Philadelphia.

MÉNIÈRE'S DISEASE AND ITS SURGICAL TREATMENT: REPORT OF 300 CASES. F. CASTELLANO, J. Neurosurg. **8**:173, 1951.

A series of 300 cases of Ménière's disease is presented, with a discussion of the etiologic factors, pathologic anatomy, symptoms, objective findings, detailed operative procedure, and follow-up studies. Castellano points out that surgical treatment is indicated in Ménière's disease (1) in all cases in which medical treatment has not produced improvement and (2) in cases in which the working capacity is impaired as a result of the severity of symptoms.

In 254 cases operation was performed. In 27 the acoustic nerve was completely sectioned; in 226 only the vestibular branch was divided; in 1 the nerve was freed from adhesions but was not sectioned.

Complete freedom from dizziness was obtained in all but eight cases; in seven of these eight patients the disease was bilateral. Tinnitus rarely disappeared. There was no operative mortality. Facial paralysis occurred in 16 cases, being transient in 14 and permanent in 2. Postoperative extradural hematoma occurred in five cases; in one of these an intracerebellar hematoma also occurred. Follow-up periods varied from a few months to 19 years.

ALPERS, Philadelphia.

PREFRONTAL LEUCOTOMY IN CHILDREN AND ADOLESCENTS. M. YAHN and S. KRYNSKI, Arq. Assist. psicopat. estad. São Paulo **16**:15, 1951.

Prefrontal lobotomy was performed on 11 girls, from 9 to 15 years of age, who presented severe behavior problems. The patients were difficult to manage, aggressive, emotionally unstable, and occasionally agitated and had perversions and antisocial tendencies. They had been observed daily in a hospital for about a year. They did not respond to other methods of treatment. The technique of lobotomy used was that of Freeman and Watts. In two patients it was impossible to operate on both sides. Epilepsy, mental deficiency, and psychopathic personality were represented. The following symptoms were improved by the operation: exhibitionism, destructive tendencies, perversions, impulsiveness, overtalkativeness, epileptic attacks, bouts of anxiety, tendency to anger readily, attempts to escape, and indifference. The results were satisfactory, especially in the psychopathic personalities, and the epileptic patients. One patient with psychopathic personality exhibited striking improvement, with social readjustment. Six patients showed marked improvement, which usually consisted in diminution of agitation and antisocial behavior, with a more satisfactory intramural adjustment. Two of the patients were not benefited at all. Two died as a result of postoperative hemorrhage. The authors recommend the use of lobotomy for agitation, antisocial tendencies, and other disturbances in behavior which cannot be controlled in any other way. The series of patients reported is small, but it does indicate the therapeutic possibilities of lobotomy. The authors believe that the sequelae of the operation itself should be less severe in younger patients.

N. SAVITSKY, New York.

HEMISPHERECTOMY AS TREATMENT OF CONVULSIONS DUE TO CEREBRAL HEMIATROPHY IN INFANTILE HEMIPLEGIA. S. OBRADOR ALCADE, Arq. neuro-psiquiat. **9**:191, 1951.

The first case of infantile hemiplegia in which an atrophied hemisphere was removed because of convulsions was reported by Obrador Alcade (*Rev. clín. españ.* **36**:172, 1950). In the patient, a girl aged 17, seizures and electroencephalographic changes disappeared in the opposite hemisphere after the operation. Three other patients, 5, 7, and 11 years old, underwent hemispherectomy. All had infantile hemiplegia and epileptic attacks. In two of these patients the hemiplegia was on the left side, and in one, on the right side. All were mentally retarded. All showed electroencephalographic changes on both sides before operation; these changes were somewhat more conspicuous over the atrophied hemisphere. One of the four patients died after the operation. There was no intensification of the hemiplegia in any instance. In a 5-year-old child removal of the left hemisphere was not followed by aphasia; apparently the right hemisphere took over the language function immediately. After the operation seizures disappeared in all the patients, even though no medication was used. Two patients were followed for 20 and 4 months, respectively. The electroencephalogram became normal on the affected side after the operation. The author recommends this operative procedure as a valuable addition to the treatment of convulsions in this condition.

N. SAVITSKY, New York.

TREATMENT OF MÉNIÈRE'S SYNDROME WITH HIGH-FREQUENCY SOUND WAVES. C. WIETHE, Wien. med. Wchnschr. **61**:466 (July 29) 1949.

Since direct surgical intervention on the labyrinth is extremely difficult, and not always satisfactory, Wiethe used high-frequency sound waves (oscillations at over 300,000 hertzian [electric] waves per second) in the treatment of 26 patients with Ménière's syndrome. The advantage of this treatment lies in the possibility of pinpointing the otherwise inaccessible structures and of modifying the frequency of the sound wave and thereby the therapeutic effect. The

desired effect is probably due to rhythmic rarification and condensation of the molecular structure of the tissues, as well as to the production of heat.

The treatment was administered every day or on alternate days for an average of 10 doses. The follow-up observations of 2 to 12 months showed 18 patients to be completely free of attacks; 6 had occasional episodes at much greater intervals, and the condition of 2 remained unchanged. The tinnitus was lost in 9 patients, improved in 10 patients, and unchanged in 5 patients. There was subjective improvement of hearing in 10 patients, while the remaining 16 reported no change. Audiometer studies showed improvement of hearing in 6 patients and some improvement (not noticed by the patient) in one case; no change was discerned in 19 patients. The caloric and rotatory tests showed only slight changes.

MASON, New York.

Muscular System

MALIGNANT TUMOR OF THE THYMUS GLAND, MYASTHENIA GRAVIS DEVELOPING AFTER REMOVAL. J. B. FERSHTAND and R. B. SHAW, Ann. Int. Med. **34**:1025, 1951.

A case of malignant tumor of the thymus gland is presented. The patient showed the involvement of the cardiac structures usually reported in cases of sarcoma arising from this gland. The case is unique in that symptoms of myasthenia gravis developed for the first time after subtotal removal of the tumor. The patient had had a known, but symptomless intrathoracic tumor (believed to be a dermoid of the anterior mediastinum) for 10 years. In spite of the massive involvement of the cardiac musculature and the myasthenia gravis, the patient lived one year after operation. The large amount of roentgen radiation he received is believed to have contributed to his partial recovery and materially prolonged his life. From the fatal outcome in this case the authors reemphasize the necessity for removing symptomless intrathoracic tumors.

ALPERS, Philadelphia.

Encephalography, Ventriculography and Roentgenography

USE OF SERIAL ANGIOGRAPHY IN DIAGNOSIS OF SPACE OCCUPYING INTRACRANIAL LESIONS. H. C. VORIS, Am. J. Roentgenol. **67**:360, 1952.

Voris reports briefly 11 cases in which serial cerebral angiography was performed. In most of the cases the percutaneous method was used, with 35% iodopyracet as the medium. Voris' routine in most cases was to take a series of six films during a period of 4½ seconds in both the anteroposterior and the lateral projection. For each series of six films 10 cc. of iodopyracet was used. Preparation for the percutaneous injection consisted of a test for sensitivity to iodopyracet and the administration of 0.3 gm. of pentobarbital sodium from 60 to 90 minutes before the procedure.

The article illustrates the various types of displacement of the cerebral blood vessels by space-occupying intracranial lesions. The necessity of both anteroposterior and lateral films is emphasized. Voris points out that the demonstration of the arterial supply and the venous drainage of vascular neoplasms of the brain is of great aid in planning the surgical procedure.

WEILAND, Philadelphia.

FIBROUS DYSPLASIA OF THE SKULL. W. FEIRING, E. H. FEIRING, and L. M. DAVIDOFF, J. Neurosurg. **8**:377, 1951.

The authors review the pathologic, clinical, and roentgenographic aspects of fibrous dysplasia, with special emphasis on cranial involvement. They discuss also the probable relation of this disease to leontiasis ossea and fibro-osseous tumors of the skull. They report five cases of fibrous dysplasia of the skull. Two were definitely of the monostatic variety and three presumably so. Symptoms referable to the eye led to neurosurgical consultation in three instances. The lesion was accidentally disclosed in one case when roentgenograms were taken after an injury. An operation was performed in four cases, in three of which the preoperative diagnosis was a meningioma and in one an osteoma. In the remaining case the diagnosis was established on clinical grounds and was subsequently verified histologically. Unilateral exophthalmos was observed in three of the cases in which operation was performed, and optic atrophy, in

one. The symptoms of the patient not operated upon were deformity of the skull and unilateral impairment of hearing. When first seen by the authors, two of the patients were in the first decade of life, one in the second, and two in the third. The roentgenographic appearance in three cases was that of a sharply localized calcific mass in the anterior fossa.

The authors point out that involvement of the skull is known to occur frequently in polyostotic fibrous dysplasia. At times, however, the skull appears to be exclusively affected by this disease. In cases of cranial involvement, particularly when the base of the skull is the site of the lesion, localized clinical symptoms may be present. Ocular manifestations are especially likely to be prominent. Confusion may arise in distinguishing between localized fibrous dysplasia and the bony changes associated with a meningioma. One of the most valuable differential criteria is the age of the patient. Fibrous dysplasia is a disorder of childhood and adolescence. Meningiomas as a rule occur during adult life.

The cause of fibrous dysplasia is unknown, and there is no specific treatment. Progressive exophthalmos and compression of cranial nerves may call for neurosurgical intervention.

ALPERS, Philadelphia.

MYELOGRAPHIC DIAGNOSIS OF SACRAL PERINEURIAL CYST. L. E. TAHERI, P. RIEMENSCHNEIDER and A. ECKER, J. Neurosurg. **9**:93, 1952.

Sacral perineurial cyst may be a possible cause of symptoms referable to the cauda equina. The symptoms include lumbosciatic pain and urinary retention. Myelography has been considered of no value in cases of this lesion because of the frequent lack of communication between the cyst and the subarachnoid space. The authors here present a case of multiple sacral perineurial cyst in which such communication was present and in which myelography permitted preoperative diagnosis.

ALPERS, Philadelphia.

RADIATION THERAPY OF THE NON-TRAUMATIC PAINFUL SHOULDER. E. L. JENKINSON, R. C. NORMAN and J. A. WILSON, Radiology **58**:192 (Feb.) 1952.

The authors describe their methods and results in the treatment of 433 patients with painful shoulder. The term "bursitis" is used in the article to describe the symptom complex that has variously been described as peritendinitis, subdeltoid bursitis, subacromial bursitis, and supraspinatous tendinitis. The primary symptom in these cases is pain in the shoulder. The patients also have tenderness on pressure over the capsular area of the shoulder and usually exhibit limitation of motion when attempts are made to abduct the arm.

The authors recognized three types for purposes of classification: acute bursitis, chronic bursitis, and an acute exacerbation of chronic bursitis. If the duration of symptoms is seven days or less, the condition is considered acute; if more than seven days, chronic.

X-ray treatment was given with a 200-kv. constant potential, a Thoraeus filter, and a target-skin distance of 50 cm. The half-value layer of the beam used for treatment was 1.9 mm. Cu. The fields used were 10 by 10 cm., and the beam was centered to the point of maximal tenderness. Daily treatments of 200 r, measured in air, were given for six days. Four of these treatments were given to an anterior field, and two, to a posterior one.

There were eighty-five patients in the acute group. Seventy of these obtained complete relief of symptoms, and 1 had no relief; all the rest had partial relief, of various degrees. Of 195 patients in the chronic group, 44 had complete relief, and 18 had none. Of 38 patients with acute exacerbations of chronic bursitis, 24 were completely relieved of all acute symptoms, and 2 had no relief.

WEILAND, Philadelphia.

News and Comment

ILLINOIS DEPARTMENT OF PUBLIC WELFARE

Immediate employment with the Illinois Department of Public Welfare is being offered physicians, psychiatrists, and tuberculosis-control physicians who pass current state civil-service examinations. State residence is not necessary.

Starting salary for Physician I is $450. Physicians eligible for a limited license under the state's new Limited Licensure Act are employed at $380. Psychiatrists I and tuberculosis-control physicians I receive a starting salary of $500.

Candidates for all three positions take an oral test and are rated on their training and experience. Those who pass both parts of the examination and have a valid Illinois license to practice medicine are offered positions immediately.

Advantages offered civil-service employees with the State of Illinois include promotional opportunities, low-cost living, paid vacations, regular hours, pay increases, and liberal retirement benefits. In addition, physicians and psychiatrists who satisfactorily complete three years of service with the Department of Public Welfare are eligible for an educational leave of absence with full pay to conduct research or educational projects approved by the Department.

Application forms may be obtained from the Illinois Civil Service Commission, Armory Building, Springfield, Ill.

AMERICAN ACADEMY OF FORENSIC SCIENCES

The American Academy of Forensic Sciences announces its fifth annual meeting, to be held Feb. 26, 27, and 28, 1953, at the Drake Hotel, Chicago. All persons planning to present papers should submit their titles to Dr. Milton Helpern, program chairman, 106 E. 85th St., New York 28, before Dec. 1, 1952.

AMERICAN PSYCHOSOMATIC SOCIETY

The American Psychosomatic Society will hold its tenth annual meeting at Chalfonte-Haddon Hall, in Atlantic City, N. J., on Saturday and Sunday, May 2 and 3, 1953.

The program committee would like to receive titles and abstracts of papers for consideration for the program, by Dec. 1, 1952. The time allotted for the reading of each paper will be twenty minutes. The committee is interested in investigations in the theory and practice of psychosomatic medicine as applied to adults and children in all the medical specialties, and in contributions in psychophysiology and ocology. One panel will be devoted to the adrenal cortex. Abstracts of contributions to this panel will be considered by the committee. Papers accepted for presentation at the meeting will be submitted to the editorial board of *Psychosomatic Medicine* for possible publication in the journal.

Material for consideration by the program committee should be sent, in duplicate, to Dr. Sydney G. Margolin, chairman, 551 Madison Ave., New York 22.

AMERICAN PSYCHIATRIC ASSOCIATION

Dr. Winfred Overholser, superintendent, St. Elizabeths Hospital, Washington, D. C., will deliver a series of four Isaac Ray Lectures on psychiatry and the law at Harvard University Law and Medical Schools in November, 1952. Dr. Overholser was selected for the honor as the first winner of the American Psychiatric Association's Isaac Ray Award for his notable contributions to the field of legal problems connected with mental disorders.

The first two lectures of the series, on "The Substance of Psychiatry" and "Differences of Viewpoint," will be presented in the courtroom at Harvard Law School at 4 p. m. on Nov. 13 and 14. The remaining two lectures, on "The Mental Patient and the Hospital" and "The Psychiatrist as Witness," will be given at 5 p. m. each day on Nov. 17 and 18 in Amphitheatre D at Harvard Medical School.

The award named in honor of Dr. Isaac Ray, a founder of the American Psychiatric Association, also carries with it an honorarium of $1,000. Establishment of the award was due

largely to the efforts of Dr. Gregory Zilboorg, prominent New York City psychiatrist and chairman of the Committee on the History of Psychiatry of the American Psychiatric Association.

Dr. Overholser is former Commissioner of Mental Diseases for Massachusetts. He has been superintendent of St. Elizabeths since 1937 and is also professor of psychiatry at George Washington University School of Medicine. A past president of the American Psychiatric Association, he served for many years as chairman of the American Psychiatric Association's Committee on Legal Aspects of Psychiatry. He was recently made a Chevalier of the Legion of Honor by the French Government.

The award committee which selected Dr. Overholser as the first winner is comprised of five doctors and two lawyers: Drs. Frank J. Curran, Charlottesville, Va., chairman; George S. Stevenson, New York; Leroy Maeder, Philadelphia; Francis J. Braceland, Hartford, Conn., and Paul Schroeder, Atlanta, Ga.; and lawyers Ralph C. Busser, Philadelphia, and Walter A. Edwards, Providence, R. I.

THE NEW YORK SOCIETY OF NEUROSURGERY

Dr. Herbert Olivecrona, professor of neurosurgery, Stockholm, will deliver the annual Charles A. Elsberg Lecture, established by The New York Society of Neurosurgery, on Monday, Dec. 1, 1952, at the New York Academy of Medicine, 2 E. 103 St., New York, at 8:30 p. m. Dr. Olivecrona has chosen for his subject, "Hypophysectomy in Man."

Books

The Battle for Mental Health. By James Clark Moloney, M.D. Price, $3.50. Pp. 98; no illustrations. Philosophical Library, Inc., 15 E. 40th St., New York, 1952.

The author states that modern psychiatry understands mental illness better than it understands mental health. He then points out that mental health to the social scientist is the most frequently occurring type for the aggregate of human beings under study. The sociologist merely fractionates culture but does not reveal the dynamics of mental health.

To the author, man is essentially the same the world over, and the characteristics of mental health are applicable to man wherever he may be found, regardless of his race, stature, color, or culture. From a dynamic viewpoint the author describes mental health as adequacy in thinking and feeling at each stage of development; the most important ingredient is appropriate spontaneity and the ability to adjust to life resiliently. Acuity with all five senses, prompt meaningful memory recall, and readiness with appropriate responses are listed with many other characteristics of mental health.

The writer furnishes many interesting statistics about mental illness and indicates that the United States is a very disorganized nation with regard to mental health.

The real battle for mental health is produced because man, owing to his fears, clings to legends and traditions. Insecurity prevents man from changing. A change represents to him a deviation from "sameness." He therefore interferes with the natural responses of the child and conditions him into a neurotic conformity.

To change these conditions, the author pleads with mothers, obstetricians, and maternity ward supervisors to break with tradition and to abandon the separation of the newborn infant from his mother, and shows how this can be done practically.

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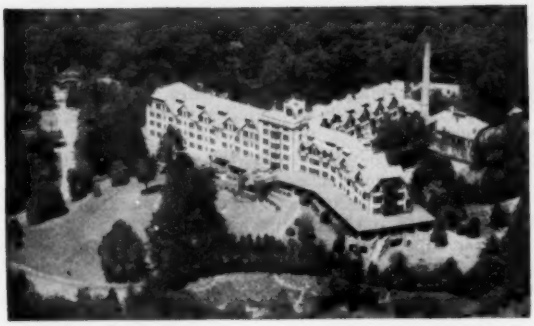

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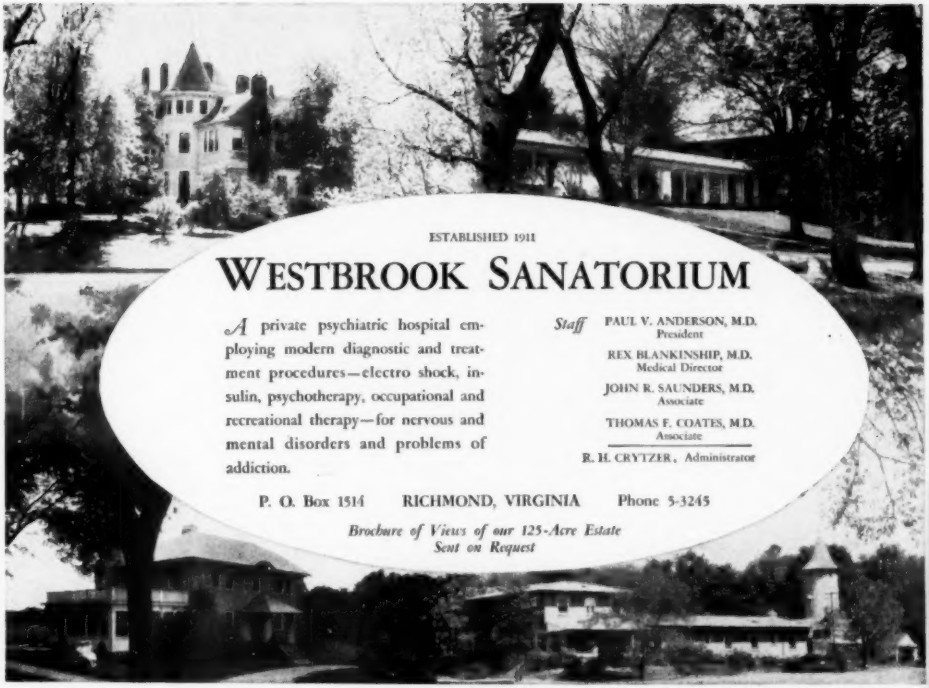
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